US009092391B2

(12) **United States Patent**
Stephan et al.

(10) **Patent No.: US 9,092,391 B2**
(45) **Date of Patent: Jul. 28, 2015**

(54) **GENETIC ANALYSIS SYSTEMS AND METHODS**

(75) Inventors: **Dietrich A. Stephan**, Phoenix, AZ (US); **Melissa Floren Filippone**, New York, NY (US); **Jennifer Wessel**, San Francisco, CA (US); **Michele Cargill**, Orinda, CA (US); **Eran Halperin**, Berkeley, CA (US)

(73) Assignee: **Navigenics, Inc.**, Carlsbad, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1060 days.

(21) Appl. No.: **12/516,915**

(22) PCT Filed: **Nov. 30, 2007**

(86) PCT No.: **PCT/US2007/086138**

§ 371 (c)(1), (2), (4) Date: **Jun. 24, 2010**

(87) PCT Pub. No.: **WO2008/067551**

PCT Pub. Date: **Jun. 5, 2008**

(65) **Prior Publication Data**

US 2010/0293130 A1 Nov. 18, 2010

Related U.S. Application Data

(63) Continuation of application No. 11/781,679, filed on Jul. 23, 2007, now abandoned.

(60) Provisional application No. 60/868,066, filed on Nov. 30, 2006, provisional application No. 60/951,123, filed on Jul. 20, 2007, provisional application No. 60/972,198, filed on Sep. 13, 2007, provisional application No. 60/985,622, filed on Nov. 5, 2007, provisional application No. 60/989,685, filed on Nov. 21, 2007.

(51) **Int. Cl.**

G01N 33/50 (2006.01)
G06F 19/18 (2011.01)
G06F 19/28 (2011.01)

(52) **U.S. Cl.**

CPC ***G06F 19/18*** (2013.01); *G06F 19/28* (2013.01)

(58) **Field of Classification Search**

None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,612,179	A	3/1997	Simons	
5,958,684	A	9/1999	Van Leeuwen et al.	
6,640,211	B1	10/2003	Holden	
6,703,228	B1	3/2004	Landers et al.	
6,955,883	B2	10/2005	Margus et al.	
7,072,794	B2	7/2006	Wittkowski	
7,401,026	B2	7/2008	Holden	
2002/0095585	A1	7/2002	Scott	
2002/0128860	A1	9/2002	Leveque et al.	
2002/0133495	A1*	9/2002	Rienhoff et al.	707/100
2002/0187474	A1	12/2002	Comings et al.	
2003/0040002	A1	2/2003	Ledley	
2003/0046110	A1	3/2003	Gogolak	
2003/0054381	A1	3/2003	Affourtit et al.	
2003/0104453	A1	6/2003	Pickar et al.	
2003/0108938	A1	6/2003	Pickar et al.	
2003/0135096	A1	7/2003	Dodds	
2003/0208454	A1	11/2003	Rienhoff et al.	
2003/0219776	A1	11/2003	Lalouel et al.	
2004/0002818	A1	1/2004	Kulp et al.	
2004/0115701	A1	6/2004	Comings et al.	
2004/0121320	A1	6/2004	DePhillipo et al.	
2005/0037366	A1	2/2005	Gut et al.	
2005/0064476	A1	3/2005	Huang et al.	
2005/0177397	A1	8/2005	Kane	
2005/0196770	A1	9/2005	Cox et al.	
2005/0209787	A1	9/2005	Waggener et al.	
2005/0214811	A1*	9/2005	Margulies et al.	435/6
2005/0243551	A1	11/2005	Onishi et al.	
2005/0272054	A1	12/2005	Cargill et al.	
2006/0046256	A1	3/2006	Halldorsson et al.	
2006/0051763	A1	3/2006	Loukola et al.	
2006/0160074	A1	7/2006	Dorn et al.	
2006/0166224	A1	7/2006	Norviel	
2006/0184489	A1	8/2006	Weiner et al.	
2006/0188875	A1	8/2006	Cox et al.	
2006/0240428	A1	10/2006	Itakura et al.	
2006/0257888	A1	11/2006	Zabeau et al.	
2006/0278241	A1	12/2006	Ruano	
2007/0122824	A1	5/2007	Tucker et al.	
2007/0196344	A1	8/2007	Osborne et al.	

(Continued)

FOREIGN PATENT DOCUMENTS

CA	2671267	6/2008
EP	1684202 A1	7/2006

(Continued)

OTHER PUBLICATIONS

Amundsen et al., Genetic analysis of the CD28/CTLA4/ICOS (CELIAC3) region in coeliac disease, Tissue Antigens, published online Oct. 20, 2004, vol. 64, Issue 5, pp. 593-599.*

(Continued)

Primary Examiner — Jason Sims

(57) **ABSTRACT**

The present invention provides methods of determining a Genetic Composite Index score by assessing the association between an individual's genotype and at least one disease or condition. The assessment comprises comparing an individual's genomic profile with a database of medically relevant genetic variations that have been established to associate with at least one disease or condition.

21 Claims, 87 Drawing Sheets

(56) **References Cited**

U.S. PATENT DOCUMENTS

2007/0254289	A1	11/2007	Li et al.	
2008/0004848	A1	1/2008	Avey	
2008/0108713	A1*	5/2008	Begovich et al.	514/789
2008/0131887	A1	6/2008	Stephan et al.	
2008/0261220	A1*	10/2008	Cracauer et al.	435/6
2009/0099789	A1	4/2009	Stephan et al.	
2009/0182579	A1	7/2009	Liu	
2009/0198519	A1	8/2009	Mcnamar	
2010/0042438	A1	2/2010	Moore et al.	
2010/0070455	A1	3/2010	Halperin et al.	

FOREIGN PATENT DOCUMENTS

GB	2444410		6/2008
JP	200067139		3/2000
JP	2002107366	A	4/2002
JP	2006500016		1/2006
JP	2010522537		7/2010
WO	WO 96/32502	A1	10/1996
WO	WO-01/16860		3/2001
WO	WO 01/16860	A2	3/2001
WO	WO-01/26029		4/2001
WO	WO 01/26029	A2	4/2001
WO	WO 01/16860	A3	6/2001
WO	WO 01/26029	A3	3/2002
WO	WO 02/063415	A2	8/2002
WO	WO 02/086663	A2	10/2002
WO	WO 02/086663	A3	5/2003
WO	WO 02/063415	A3	8/2003
WO	WO-2004/020968		3/2004
WO	WO 2004/072887	A2	8/2004
WO	WO-2004/109551		12/2004
WO	WO 2004/072887	A3	12/2005
WO	WO-2006/008045		1/2006
WO	WO-2006/053955		5/2006
WO	WO 2006/065658	A2	6/2006
WO	WO 2006/065658	A3	11/2007
WO	WO 2008/067551	A2	6/2008
WO	WO 2008/067551	A3	12/2008
WO	WO 2009/023360	A2	2/2009
WO	WO 2009/023360	A3	8/2009

OTHER PUBLICATIONS

Office action dated Feb. 15, 2011 for U.S. Appl. No. 11/781,679.
Office action dated Mar. 30, 2010 for U.S. Appl. No. 11/781,679.
Office action dated Jun. 15, 2009 for U.S. Appl. No. 11/781,679.
Office action dated Sep. 13, 2011 for U.S. Appl. No. 12/239,718.
Office action dated Nov. 15, 2011 for U.S. Appl. No. 12/538,064.
International preliminary report on patentability dated Feb. 17, 2011 for PCT Application No. US09/053216.
International search report dated Jan. 4, 2010 for PCT Application No. US2009/56720.
Jin, et al. Combined effects of HLA-Cw6 and cigarette smoking in psoriasis vulgaris: a hospital-based case-control study in China. J Eur Acad Dermatol Venereol. Feb. 2009;23(2):132-7.
Demchuck, et al. A statistical model for assessing genetic susceptibility as a risk factor in multifactorial diseases: lessons from occupational asthma. Environ Health Perspect. Feb. 2007;115(2):231-4.
Office action with search report dated Apr. 12, 2011 for Taiwanese application 096148586. (in Chinese with English summary).
Office action dated Mar. 28, 2012 for U.S. Appl. No. 11/781,679.
Office action dated Apr. 11, 2012 for U.S. Appl. No. 12/239,718.
Singapore search report and written opinion dated May 20, 2011 for Singapore Application No. 200903655-9.
Arking, et al. A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. Nature Genet. 2006; 38(6): 644-651.
Baker, et al. Association of an extended haplotype in the tau gene with progressive supranuclear palsy. Hum Molec Genet. 1999; 8(4): 711-5.
Begovich, et al. A Missense Single-Nucleotide Polymorphism in a Gene Encoding a Protein Tyrosine Phosphatase (PTPN22) is Associated with Rheumatoid Arthritis. Am. J. Hum. Genet. 2004; 75: 330-337.
Bertina, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994; 369(6475): 64-67.
Bottini, et al. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. Nature Genet. 2004; 36(4): 337-338.
Brenner, S. Common sense for our genomes. Nature. 2007; 449: 783-784.
Breslin, et al. Monozygotic twins with Crohn's disease and ulcerative colitis: a unique case report. Gut. 1997; 41: 557-560.
Casas, et al. Endothelial Nitric Oxide Synthase Genotype and Ischemic Heart Disease: Meta-Analysis of 26 Studies Involving 23028 Subjects. Circulation. 2004; 109: 1359-1365.
Coon, et al. A High Density Whole-Genome Association Study Reveals that APOE is the Major Susceptibility Gene for Sporadic Late-Onset Alzheimer's Disease. Psychiatry. 2007; 68:4: 613-618.
Corder, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993; 261: 921-923.
Cox, et al. A common coding variant in CASP8 is associated with breast cancer risk. Nature Genetics. 2007; 39(3): 352-358, 688.
Crocq, et al. Association between schizophrenia and homozygosity at the dopamine D3 receptor gene. J Med Genet. 1992; 29: 858-860.
Dequervain, et al. Indentification of a genetic cluster influencing memory performance and hippocampal activity in humans. PNAS 2006; 103(11): 4270-4274.
Doh-Ura, et al. Pro→Leu change at position 102 of prion protein is the most common but not the sole mutation related to Gerstmann-Sträussler syndrome. Biochem Biophys Res Commun. 1989; 163(2): 974-979.
Duerr, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science. 2006; 314(5804): 1461-1463.
Dunsworth, et al. Heterogeneity of insulin-dependent diabetes—new evidence. Clin Genet. 1982; 21: 233-236.
Easton, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature. 2007; 447(28): 1087-1095.
Farrer, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer's disease. A meta-analysis. JAMA. 1997; 278(16): 1349-1356.
Fernandez-Arquero, et al. Primary association of a TNF gene polymorphism with susceptibility to multiple sclerosis. Neurology. 1999; 53: 1361-1363.
Frayling, et al. A Common Variant in the FTO Gene is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity. Sciencexpress. 2007; 1-5 and four unnumbered pages.
Gatz, et al. Role of Genese and Environments for Explaining Alzheimer Disease. Arch Gen Psychiatry. 2006; 63: 168-174.
Graham, et al. A common haplotype of interferon regulatory factor 5 (IRF5) regulates splicing and expression and is associated with increased risk of systemic lupus erythematosus. Nature Genet. 2006; 38: 550-555.
Grant, et al. Reduced bone density and osteoporosis associated with a polymorphic Sp1 binding site in the collagen type I α 1 gene. Nature Genet. 1996; 14: 203-205.
Grant, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nature Genet. 2006; 38: 320-323.
Greco, et al. The first large population based twin study of coeliac disease. Gut. 2002; 50: 624-628.
Green, et al. The association of HLA-linked genes with systemic lupus erythematosus. Ann Hum Genet. 1986; 50: 93-96.
Greenbaum, et al. Islet cell antibody-positive relatives with human leukocyte antigen DQA1*0102, DQB1*0602: Identification by the diabetes prevention trial-type 1. J Clin Endocr Metab. 2000; 85(3): 1255-1260.
Gregersen, et al. Functional epistasis on a common MHC haplotype associated with multiple sclerosis. Nature. 2006; 443: 574-577.
Gudmundsson, et al. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. Nature Genetics. 2007; 1-7.

(56) **References Cited**

OTHER PUBLICATIONS

Haddad, et al. The Genetics of Age-Related Macular Degeneration: A Review of Progress to Date. Survey of Ophthalmology. 2006; 51(4): 316-363.
Haiman, et al. Multiple regions within 8q24 independently affect risk for prostate cancer. Nature Genetics. 2007; 1-7.
Healey, et al. A common variant in BRCA2 is associated with both breast cancer risk and prenatal viability. Nature Genet. 2000; 26: 362-364.
Helgadottir, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science. 2007; 316(5830):1491-1493.
Heward, et al. Linkage disequilibrium between the human leukocyte antigen class II region of the major histocompatibility complex and Graves' disease: Replication using a population case control and family-based study. J Clin Endocr Metab. 1998; 83(10): 3394-3397.
Hinds, et al. Whole-genome patterns of common DNA variation in three human populations. Science. 2005; 307(5712): 1072-1079.
Hugot, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature. 2001; 411: 599-603.
Hunt, et al. A common CTLA4 haplotype associated with coeliac disease. European Journal of Human Genetics. 2005; 440-444.
International Hapmap Consortium. A haplotype of the human genome. Nature. 2005; 437(7036): 1299-1320.
Klein, et al. Complement factor H polymorphism in age-related macular degeneration. Science. 2005; 308: 385-389.
Kubo, et al. A nonsynonymous SNP in PRKCH (protein kinase C n) increases the risk of cerebral infarction. Nature Genetics. 2007; 39(2): 212-217.
Laken, et al. Familial colorectal cancer in Ashkenazim due to a hypermutable tract in APC. Nature Genet. 1997; 17: 79-83.
Lichtenstein, et al. Environmental and Heritable Factors in the Causation of Cancer. The New England Journal of Medicine. 2000; 343(2): 78-85.
Locatelli, et al. The Heritability of Breast Cancer: a Bayesian Correlated Frailty Model Applied to Swedish Twins Data. Twin Research. 2003; 7(2): 182-191.
MacGregor, et al. Characterizing the Quantitative Genetic Contribution to Rheumatoid Arthritis Using Data From Twins. Arthritis & Rheumatism. 2000; 43(1): 30-37.
Maller, et al. Common variation in three genes, including a noncoding variant in CFH strongly influences risk of age-related macular degeneration. Nature Genetics. 2006; 38(9): 1055-1059.
McGuffin, et al. The Heritability of Bipolar Affective Disorder and the Genetic Relationship to Unipolar Depression. Arch Gen Psychiatry. 2003; 60: 497-502.
McPherson, et al. A Common Allele on Chromosome 9 Associated with Coronary Heart Disease. Science. 2007; 316: 1488-1491.
Michou, et al. Validation of the reshaped shared epitope HLA-DRB1 classification in rheumatoid arthritis. Arthritis Res Ther. 2006; 8(3): 1-6.
Miyamoto, et al. A functional polymophism in the 5' UTR of GDF5 is associated with susceptibility to osteoarthritis. Nature Genetics. 2007; 39(4): 529-533.
Nisticò, et al. The CTLA-4 gene region of chromosome 2q33 is linked to, and associated with, type 1 diabetes. Hum Molec Genet. 1996; 5: 1075-1080.
Nisticò, et al., Concordance, disease progression, and heritability of coeliac disease in Italian twins. Gut. 2006; 55: 803-808.
Page, et al. Heredity and Prostate Cancer: A Study of World War II Veteran Twins. The Prostate. 1997; 33: 240-245.
Page, et al. Primary Osteoarthritis of the Hip in Monozygotic and Dizygotic Male Twins. Twin Research. 2003; 6(2): 147-151.
Papassotiropoulos, et al. Common Kibra alleles are associated with human memory performance. Science. 2006; 314: 475-478.
Pugliese, et al. The insulin gene is transcribed in the human thymus and transcription levels correlate with allelic variation at the INS VNTR-IDDM2 susceptibility locus for type 1 diabetes. Nature Genet. 1997; 15: 293-297.
Reiman, et al. GAB2 Alleles Modify Alzheimer's Risk in APOE g4 Carriers. Neuron. 2007; 54: 713-720.
Roberts, et al. Personalized Genomic Medicine: a Future Prerequisite for the Prevention of Coronary Artery Disease. Am Heart Hosp J. 2006; 4: 222-227.
Samson, et al. Resistance to HIV-1 infection in caucasian individuals-bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature. 1996; 382: 722-725.
Scott, et al. A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants. Science. 2007; 316: 1341-1345.
Sladek, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature. 2007; 445: 881-885.
Smyth, et al. A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. Nature Genet. 2006; 38: 617-619.
Stacey, et al. Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer. Nature Genetics. 2007; 39: 865-869.
Steinthorsdottir, et al. A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. Nature Genetics. 2007; 39(6): 770-775.
Tambs, et al. Genetic and Environmental Contributions to the Variance of the Body Mass Index in a Norwegian Sample of First- and Second-Degree Relatives. American Journal of Human Biology. 1991; 3: 257-267.
Thorisson, et al. A User's Guide to the International HapMap Project Web Site. International Haplotype Map Project. 2003; 1-11.
Topol, et al. Single Nucleotide Polymorphisms in Multiple Novel Thrombosponding Genes May Be Associated With Familial Premature Myocardial Infarction. Circulation. 2001; 104: 2641-2644.
Van Heel, et al. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. Nature Genetics. 2007; 39(7): 827-829.
Van Tilburg, et al. Defining the genetic contribution of type 2 diabetes mellitus. J. Med. Genet. 2001; 38: 569-578.
Walsh, et al. An integrated haplotype map of the human major histocompatibility complex. Am J Hum Genet. 2003; 73: 580-590.
Wellcome Trust Case Control Consortium, The Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007; 447: 661-678.
Witte, J. S. Multiple prostate cancer risk variants on 8q24. Nature Genetics. 2007; 39(5): 579-580.
Yeager, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24, Nature Genetics. 2007; 1-5.
Yoshida, et al. Determination of genotypes of human aldehyde dehydrogenase ALDH2 locus. Am J Hum Genet. 1983; 35: 1107-1116.
Zdravkovic, S. Coronary Heart Disease in Swedish Twins: Quantitative Genetic Studies. Karolinska Institutet. 2006; 1-39.
Zeggini, et al. Replication of Genome-Wide Association Signals in UK Samples Reveals Risk Loci for Type 2 Diabetes. 2007; 316: 1336-1341.
Zhai, et al. Genetic influence on the progression of radiographic knee osteoarthritis: a longitudinal twin study. OsteoArthritis and Cartilage. 2007; 15(2): 222-225.
European search rerport and search opinion dated Aug. 4, 2011 for Application No. 08834363.7.
Goddard, et al. Linkage disequilibrium and allele-frequency distributions for 114 single-nucleotide polymorphisms in five populations. Am J Hum Genet. Jan. 2000;66(1):216-34.
Lazarus, et al. Single-nucleotide polymorphisms in the interleukin-10 gene: differences in frequencies, linkage disequilibrium patterns, and haplotypes in three United States ethnic groups. Genomics. Aug. 2002;80(2):223-8.
Lo, et al. GABRB2 association with schizophrenia: commonalities and differences between ethnic groups and clinical subtypes. Biol Psychiatry. Mar. 1, 2007;61(5):653-60. Epub Sep. 1, 2006.
Nuchnoi, et al. Linkage disequilibrium structure of the 5q31-33 region in a Thai population. J Hum Genet. 2008;53(9):850-6. Epub Jun. 24, 2008.
Office action dated Aug. 24, 2011 for EP Application No. 09792478.1.

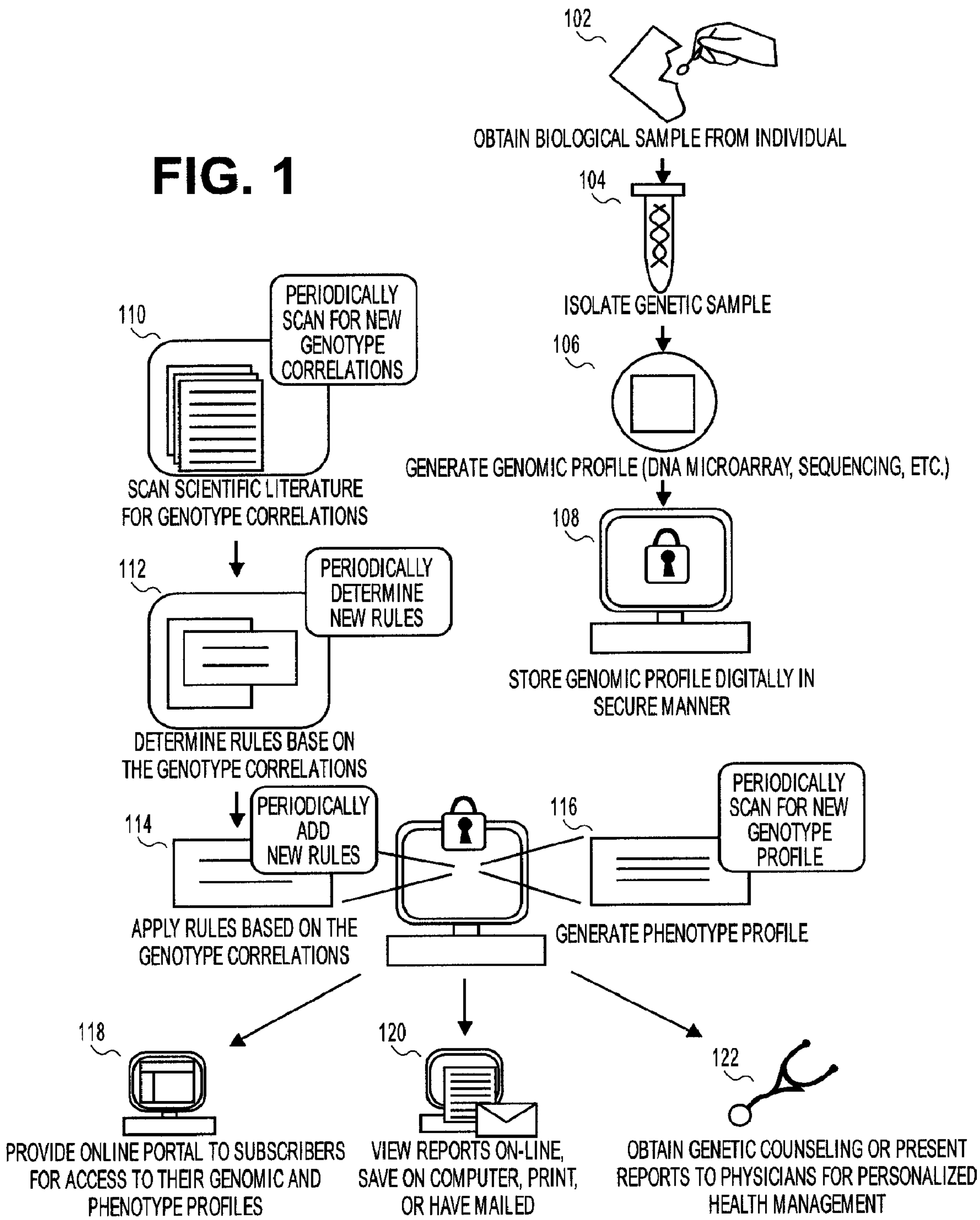
(56) **References Cited**

OTHER PUBLICATIONS

Rao, et al. Single nucleotide polymorphisms in alcohol dehydrogenase genes among some Indian populations. Am J Hum Biol. May-Jun. 2007;19(3):338-44.
European search report and opinion dated Oct. 20, 2010 for Application No. 07854875.7.
Hamosh, et al. Online Mendelian Inheritance in Man (OMIM). Hum Mutat. 2000;15(1):57-61.
Padhukasahasram, et al. Presymptomatic risk assessment for chronic non-communicable diseases. PLoS One. Dec. 31, 2010;5(12):e14338.
Discovery Vitality HealthyFood Catalogue. Feb. 2009. Available at https://healthyfood.prezence.co.za/Discovery__Vitality__HealthyFood__Catalog.pdf. Accessed Aug. 13, 2009.
Discovery Vitality program, "HealthyFood Overview." Available at https://www.discovery.co.za/memberf.jhtml?p__brand__css=/StyleSheets/screen__vitality.css &p__content=/content/view__content.jhtml&p__template=1&p__alias=indv__discovery__vitality&p__path=healthyfood/healthyfood__overview/healthyfood.xml. Accessed Aug. 13, 2009.
Discovery Vitality program, "How to Earn Points." Available at https://www.discovery.co.za/memberf.jhtml?p__brand__css=/StyleSheets/screen__vitality.css&p__content=/content/view__content.jhtml&p__template=5&p__alias=indv__discovery__vitality__howto&p__path=how__to__earn__points.xml&p__children=how__to__earn__points__contents. Accessed Aug. 13, 2009.
Discovery Vitality program, "Other preventive screening tests." Available at https://www.discovery.co.za/index__login.jhtml?p__content=/content/view__content.jhtml&p__alias=indv__discovery__vitality__howto&p__path=how__to__earn__points__contents/vitality__screenings__other.xml&p__brand__css=/StyleSheets/screen__vitality.css. Accessed Aug. 13, 2009.
Discovery Vitality program, "Virgin Life Care HealthZone." Available at https://www.discovery.co.za/index__login.jhtml?p__content=/content/view__content.jhtml&p__alias=indv__discovery__vitality__howto&p__path=how__to__earn__points__contents/virgin__life__care__healthzones.xml&p__brand__css=/StyleSheets/screen__vitality.css. Accessed Aug. 13, 2009.
Discovery Vitality program, "Vitality Fitness Assessment." Available at https://www.discovery.co.za/index__login.jhtml?p__content=/content/view__content.jhtml&p__alias=indv__discovery__vitality__howto&p__path=how__to__earn__points__contents/vitality__fitness__assessment.xml&p__brand__css=/StyleSheets/screen__vitality.css. Accessed Aug. 13, 2009.
Discovery Vitality program, "Vitality Nutrition Assessment." Available at https://www.discovery.co.za/index__login.jhtml?p__content=/content/view__content.jhtml&p__alias=indv__discovery__vitality__howto&p__path=how__to__earn__points__contents/nutrition__assesment.xml&p__brand__css=/StyleSheets/screen__vitality.css. Accessed Aug. 13, 2009.
Discovery Vitality program, "Vitality pharmacy screenings." Available at https://www.discovery.co.za/index__login.jhtml?p__content=/content/view__content.jhtml&p__alias=indv__discovery__vitality__howto&p__path=how__to__earn__points__contents/vitality__pharmacy__screenings.xml&p__brand__css=/StyleSheets/screen__vitality.css. Accessed Aug. 13, 2009.
Discovery Vitality program, "Vitality's online Nutrition Centre." Available at https://www.discovery.co.za/index__login.jhtml?p__content=/content/view__content.jhtml &p__alias=indv__discovery__vitality__howto&p__path=how__to__earn__points__contents/nutrition__centre.xml&p__brand__css=/StyleSheets/screen__vitality.css. Accessed Aug. 13, 2009.
Discovery Vitality program, "Vitality's online Stress Centre." Available at https://www.discovery.co.za/index__login.jhtml?p__content=/content/view__content.jhtml&p__alias=indv__discovery__vitality__howto&p__path=how__to__earn__points__contents/stress__management__centre.xml&p__brand__css=/StyleSheets/screen__vitality.css. Accessed Aug. 13, 2009.
Discovery Vitality program, "What is Vitality?" Available at https://www.discovery.co.za/index__login.jhtml?p__brand__css=/StyleSheets/screen__vitality.css&p__content=/content/view__content.jhtml&p__template=1&p__alias=indv__discovery__vitality&p__path=what__is__vitality/what__is__vitality.xml. Accessed Aug. 13, 2009.
Hilton Breakfast color-coded guide. Available at http://www.hilton.com/en/hi/promotions/hiltonbreakfast/index.jhtml?cid=OH,HH,houwc,BreakfastF. Accessed Aug. 13, 2009.
International search report dated Jan. 9, 2009 for PCT Application No. US08/78035.
International search report dated Oct. 1, 2008 for PCT Application No. US07/86138.
International search report dated Oct. 2, 2009 for PCT Application No. US09/053216.
Search Report dated Feb. 29, 2008 for Application No. GB 0723512.0.
Lewis, C., "Genetic association studies: Design, analysis and interpretation", *Briefings in Bioinformatics*, vol. 3(2), Jun. 2002, 146-153.
"Subscription" Google Dictionary, http://www.google.com/search?q=subscription+definition&sourceid=ie7 &rls=com.microsoft: en-us: IE-SearchBox&ie=&oe= (last visited Nov. 1, 2012).

* cited by examiner

FIG. 1


102
OBTAIN BIOLOGICAL SAMPLE FROM INDIVIDUAL
104
ISOLATE GENETIC SAMPLE
106
GENERATE GENOMIC PROFILE (DNA MICROARRAY, SEQUENCING, ETC.)
108
STORE GENOMIC PROFILE DIGITALLY IN SECURE MANNER
110
PERIODICALLY SCAN FOR NEW GENOTYPE CORRELATIONS
SCAN SCIENTIFIC LITERATURE FOR GENOTYPE CORRELATIONS
112
PERIODICALLY DETERMINE NEW RULES
DETERMINE RULES BASE ON THE GENOTYPE CORRELATIONS
114
PERIODICALLY ADD NEW RULES
APPLY RULES BASED ON THE GENOTYPE CORRELATIONS
116
PERIODICALLY SCAN FOR NEW GENOTYPE PROFILE
GENERATE PHENOTYPE PROFILE
118
PROVIDE ONLINE PORTAL TO SUBSCRIBERS FOR ACCESS TO THEIR GENOMIC AND PHENOTYPE PROFILES
120
VIEW REPORTS ON-LINE, SAVE ON COMPUTER, PRINT, OR HAVE MAILED
122
OBTAIN GENETIC COUNSELING OR PRESENT REPORTS TO PHYSICIANS FOR PERSONALIZED HEALTH MANAGEMENT

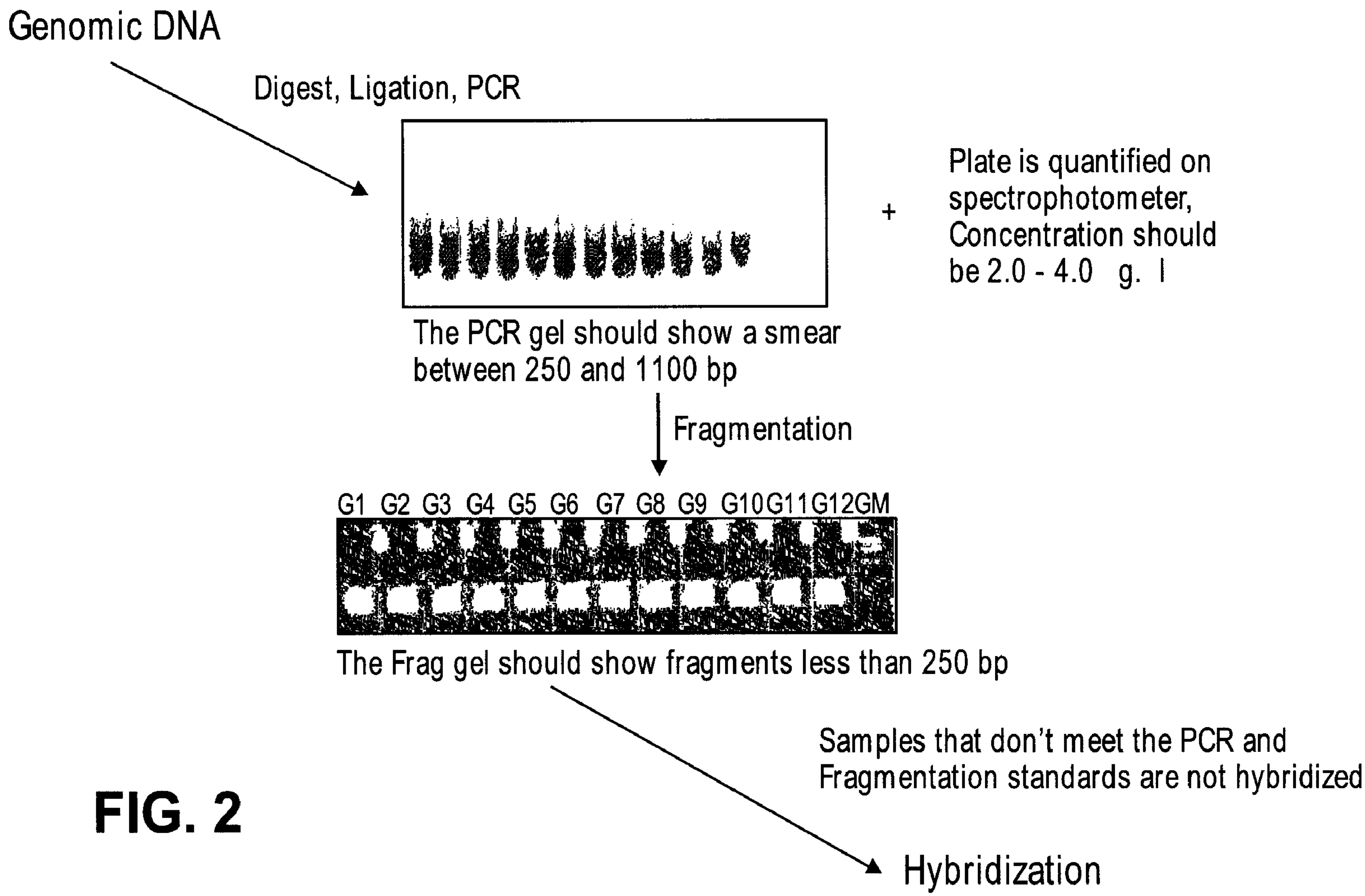
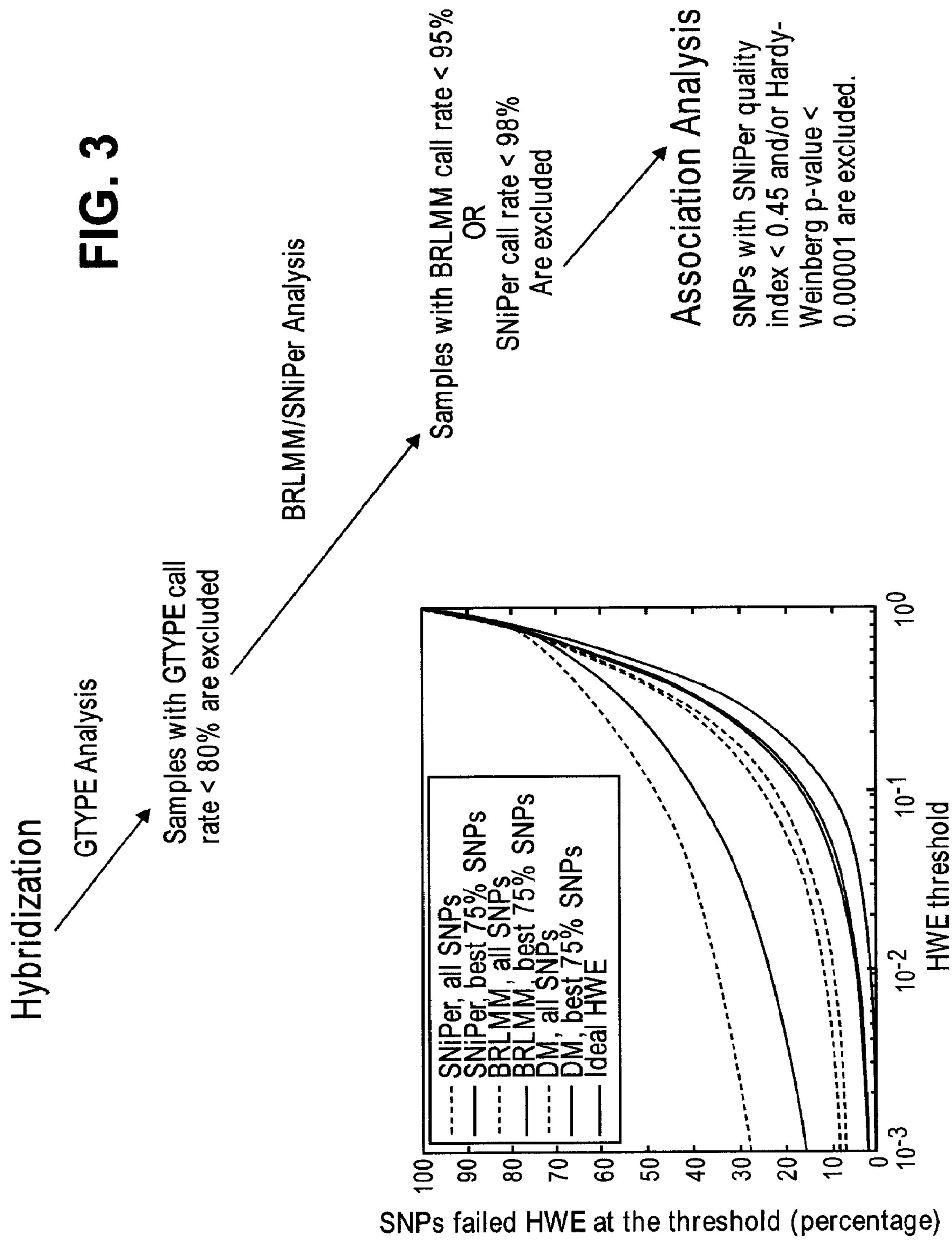

Genomic DNA
Digest, Ligation, PCR
+
Plate is quantified on spectrophotometer, Concentration should be 2.0 - 4.0 g. l
The PCR gel should show a smear between 250 and 1100 bp
Fragmentation
G1 G2 G3 G4 G5 G6 G7 G8 G9 G10 G11 G12 GM
The Frag gel should show fragments less than 250 bp
Samples that don't meet the PCR and Fragmentation standards are not hybridized
Hybridization

FIG. 2

FIG. 3


Hybridization
GTYPE Analysis
Samples with GTYPE call rate < 80% are excluded
BRLMM/SNiPer Analysis
Samples with BRLMM call rate < 95%
OR
SNiPer call rate < 98%
Are excluded
Association Analysis
SNPs with SNiPer quality index < 0.45 and/or Hardy-Weinberg p-value < 0.00001 are excluded.
SNiPer, all SNPs
SNiPer, best 75% SNPs
BRLMM, all SNPs
BRLMM, best 75% SNPs
DM, all SNPs
DM, best 75% SNPs
Ideal HWE
SNPs failed HWE at the threshold (percentage)
HWE threshold
0
10
20
30
40
50
60
70
80
90
100
10^{-3}
10^{-2}
10^{-1}
10^{0}

Short Phenotype Name	Locus	Gene (anchaloc on B36)	Gender applicability (F, M, B)	Test SNP	CHR	B3S Location	Test Risk Allele (plus, R)	Test NonRisk Allele (plus, N)	Ethnicity Race-distr
AD	AD_1	APOE	B	rs4420638	chr19	50114785	G	A	CEU
BC	BC_1	FGFR2	F	rs2981582	chr10	123342306	T	C	CEU/AS
BC	BC_2	TNRC9	F	rs3803662	chr16	51143841	T	C	CEU/AS
BC	BC_3	MAP3K1	F	rs4700485	chr5	56067640	G	A	CEU/AS
BC	BC_4	LSP1	F	rs3817198	chr11	1865581	C	T	CEU/AS
BC	BC_5	CASP8	F	rs17468277	chr2	201857833	C	T	CEU
BCERP	BCERP_1	chr2.217614077	F	rs6721996	chr2	217614076	G	A	CEU
BCERP	BCERP_2	TNRC9	F	rs3803662	chr16	51143841	T	C	CEU
BMIOB	BMIOB_1	FTO	B	rs9939609	chr16	52378027	A	T	CEU
BMIOW	BMIOW_1	FTO	B	rs9939609	chr16	52378027	A	T	CEU
BP	BP_1	PALB2	B	rs420259	chr16	23541526	T	C	CEU
CD	CD_1	chr10.101277754	B	rs1088365	chr10	101277754	G	A	CEU
CD	CD_2	PTGER4	B	rs17234657	chr5	404037265	G	T	CEU
CD	CD_3	ATG16L1	B	rs10210302	chr2	233823577	T	C	CEU
CD	CD_4	BSN	B	rs9858542	chr3	49676986	A	G	CEU
CD	CD_5	IL23R	B	rs11805303	chr1	67448103	T	C	CEU
CD	CD_6	IRGM	B	rs1000113	chr5	150220268	T	C	CEU
CD	CD_7	NOD2 (CARD15)	B	rs17221417	chr16	49297082	G	C	CEU
CD	CD_8	PTPN2	B	rs2542151	chr18	12769946	G	T	CEU
CD	CD_9	ZNF365	B	rs10761659	chr10	64115569	G	A	CEU
CelD	CelD_1	IL2-IL22 Locus	B	rs6840978	chr4	123774157	C	T	CEU
CelD	CelD_2	HLA-DQ2.5cis	B	rs2187668	chr6	32713862	A	G	CEU
CelD	CelD_3	CTLA4	B	rs11571315	chr2	204442732	A	G	CEU
EMI	EMI_1	THBS4	B	rs1866389	chr5	79397020	C	G	CEU

FIG. 4A

Short Phenotype Name	Locus	Gene (anchaloc on B36)	Gender applicability (F, M, B)	Test SNP	CHR	B3S Location	Test Risk Allele (plus, R)	Test NonRisk Allele (plus, N)	Ethnicity Race-distr
EMI	EMI_2	9p21	B	rs1333049	chr9	22114476	C	G	CEU
MI	MI_1	9p21	B	rs1333049	chr9	22114476	C	G	CEU
OAK	OAK_1	GDF5	B	rs4911178	chr20	33489396	A	G	CHB
PC	PC_1	8q24_R1	M	rs9643226	chr8	128563663	C	G	CEU
PC	PC_2	8q24_R3	M	rs6983267	chr8	128482487	G	T	CEU
RA	RA_1	PTPN22	B	rs6679677	chr1	114105330	A	C	CEU
RA	RA_2	MHC	B	rs6457617	chr6	32771828	T	C	CEU
T2D	T2D_1	CDKAL1	B	rs7754840	chr6	20769228	C	G	CEU
T2D	T2D_10	TCF7L2	B	rs4506565	chr10	114746030	T	A	CEU
T2D	T2D_2	CDKAL1	B	rs7756992	chr6	20787687	G	A	CHB
T2D	T2D_2	CDKAL1	B	rs7756992	chr6	20787687	G	A	CEU
T2D	T2D_3	CDKN2A/B	B	rs10811661	chr9	22124093	T	C	CEU
T2D	T2D_4	Chr11.41871942	B	rs12804210	chr11	41871941	T	C	CEU
T2D	T2D_5	FTO	B	rs8050136	chr16	52373775	A	C	CEU
T2D	T2D_6	HHEX	B	rs1111875	chr10	94452861	G	A	CEU
T2D	T2D_7	IGF2BP2	B	rs4402960	chr3	186994380	T	G	CEU
T2D	T2D_8	KCNJ11	B	rs5215	chr11	17366147	C	T	CEU
T2D	T2D_9	PPARG	B	rs1801282	chr3	12368124	C	G	CEU
AMD	AMD_1	GRK5	B	rs1537576	chr10	39926059	C	G	CEU
AMD	AMD_2	LOC387715	B	rs10490924	chr10	124204438	T	G	CEU
AMD	AMD_3	CFH	B	rs10737680	chr1	194946078	C	A	CEU
AMD	AMD_4	CFB-C2	B	rs541862	chr6	32024930	A	G	CEU

FIG. 4B

Short Phenotype Name	Gene (or chr.loc on B36)	Functional on published SNP	Published Risk allele (plus)	Published Non Risk allele (plus)	UNITS for effect estimate	Effect Estimate	Genotypic risk: risk homoz (RR vs NN)	Genotypic risk heteroz (RN vs NN)
AD	APOE	rs429358 & rs7412 (ApoE2/3/4 SNPs)	C	T	OR (95% CI)	genotypic	21.59 (9.88, 47.21	5.02 (3.72, 6.77)
BC	FGFR2	rs2981582	T	C	OR (95% CI)	genotypic	1.63 (1.51, 1.72)	1.23 (1.18, 1.28)
BC	TNRC9	rs3803662	T	C	OR (95% CI)	genotypic	1.39(1.26, 1.45)	1.23(1.18, 1.29)
BC	MAP3K1	rs889312	C	A	OR (95% CI)	genotypic	1.13(1.09, 1.18)	1.13(1.10, 1.16)
BC	LSP1	rs3817198	C	T	OR (95% CI)	genotypic	1.17(1.08, 1.25)	1.06(1.02, 1.11)
BC	CASP8	rs1045485	G	C	OR (95% CI)	genotypic	1.35(1.04, 1.18)	1.12(1.15, .61)
BCERP	chr2.217614077	rs13387042	A	G	OR (95% CI)	genotypic	1.44(1.30, 1.58)	1.11(1.03, 1.20)
BCERP	TNRC9	rs3803662	T	C	OR (95% CI)	genotypic	1.64(1.45, 1.85)	1.27(1.19, 1.36)
BMIOB	FTO	rs9939609	A	T	OR (95% CI)	genotypic	1.74(1.60, 1.89)	1.31(1.23, 1.39)
BMIOW	FTO	rs9939609	A	T	OR (95% CI)	genotypic	1.42(1.32, 1.52)	1.17(1.11, 1.23)
BP	PALB2	rs420259	T	C	OR (95% CI)	genotypic	2.07(1.60, 2.69)	2.08(1.60, 2.71)
CD	chr10.101277754	rs1088365	G	A	OR (95% CI)	genotypic	1.62(1.37, 1.92)	1.2(1.03, 1.39)
CD	PTGER4	rs17234657	G	T	OR (95% CI)	genotypic	2.32(1.59, 3.39)	1.54(1.34, 1.76)
CD	ATG16L1	rs10210302	T	C	OR (95% CI)	genotypic	1.85(1.56, 2.21)	1.19(1.01, 1.41)
CD	BSN	rs9858542	A	G	OR (95% CI)	genotypic	1.84(1.49, 2.26)	1.09(0.96, 1.24)
CD	IL23R	rs11805303	T	C	OR (95% CI)	genotypic	1.86(1.54, 2.24)	1.39(1.22, 1.58)
CD	IRGM	rs1000113	T	C	OR (95% CI)	genotypic	1.92(0.92, 4.00)	1.54(1.31, 1.82)
CD	NOD2 (CARD15)	rs17221417	G	C	OR (95% CI)	genotypic	1.92(1.58, 2.34)	1.29(1.13, 1.46)
CD	PTPN2	rs2542151	G	T	OR (95% CI)	genotypic	2.01(1.46, 2.76)	1.3(1.13, 1.48)
CD	ZNF365	rs10761659	G	A	OR (95% CI)	genotypic	1.55(1.30, 1.84)	1.23(1.05, 1.45)
CelD	IL2-IL22 locus	rs6840978	C	T	OR (95% CI)	allelic		
CelD	HLA-DQ2.5cis	rs2187668	A	G	OR (95% CI)	allelic		
CelD	CTLA4	rs231779	T	C	OR (95% CI)	allelic		

FIG. 4C

Short Phenotype Name	Gene (or chr.loc on B36)	Functional on published SNP	Published Risk allele (plus)	Published Non Risk allele (plus)	UNITS for effect estimate	Effect Estimate	Genotypic risk: risk homoz (RR vs NN)	Genotypic risk heteroz (RN vs NN)
EMI	THBS4	rs1866389	C	G	OR (95% CI)	genotypic	1.64 (0.75, 3.57)	1.85(1.28, 2.67)
EMI	9p21	rs10757278	G	A	OR (95% CI)	genotypic	2.08(1.69, 2.58)	1.56(1.32, 1.85)
MI	9p21	rs10757278	G	A	OR (95% CI)	genotypic	1.72(1.45, 2.03)	1.28(1.14, 1.45)
OAK	GDF5	rs143383	T	C	OR (95% CI)	genotypic	2.04(1.16, 3.58)	1.27(0.71, 2.28)
PC	8q24_R1	rs1447295	A	C	OR (95% CI)	genotypic	1.43(1.29, 1.59)	2.23(1.58, 3.14)
PC	8q24_R3	rs6983267	G	T	OR (95% CI)	genotypic	1.26(1.13, 1.41)	1.58(1.40, 1.78)
RA	PTPN22	rs6679677	A	C	OR (95% CI)	genotypic	3.32(1.93, 5.59)	1.98(1.72, 2.27)
RA	MHC	rs6457617	T	C	OR (95% CI)	genotypic	5.21(4.31, 6.30)	2.36(1.97, 2.84)
T2D	CDKAL1	rs7754840	C	G	OR (95% CI)	genotypic	1.34(1.23, 1.47)	1.33(1.22, 1.45)
T2D	TCF7L2	rs4506565	T	A	OR (95% CI)	genotypic	1.88(1.56, 2.27)	1.36(1.20, 1.54)
T2D	CDKAL1	rs7756992	G	A	OR (95% CI)	genotypic	1.52(1.21, 1.90)	1.27(1.05, 1.55)
T2D	CDKAL1	rs7756992	G	A	OR (95% CI)	genotypic	1.50(1.31, 1.72)	1.15(1.06, 1.24)
T2D	CDKN2A/B	rs10811661	T	C	OR (95% CI)	genotypic	1.39(1.13, 1.71)	1.16(0.94, 1.43)
T2D	Chr11.41871942	rs9300039	C	A	OR (95% CI)	genotypic	2.61(1.33, 5.11)	1.80(0.91, 3.57)
T2D	FTO	rs8050136	A	C	OR (95% CI)	genotypic	1.49(1.33, 1.68)	1.15(1.06, 1.26)
T2D	HHEX	rs1111875	G	A	OR (95% CI)	genotypic	1.20(1.10, 1.31)	1.06(0.98, 1.16)
T2D	IGF2BP2	rs4402960	T	G	OR (95% CI)	genotypic	1.21(1.10, 1.34)	1.16(1.09, 1.24)
T2D	KCNJ11	rs5219	T	C	OR (95% CI)	genotypic	1.22(1.04, 1.44)	1.12(0.98, 1.28)
T2D	PPARG	rs1801282	C	G	OR (95% CI)	genotypic	1.53(1.08, 2.16)	1.30(0.91, 1.86)
AMD	GRK5	rs1537576	C	G	OR (n/a CI)	genotypic		
AMD	LOC387715	rs10490924	T	G	OR (n/a CI)	genotypic	1.9	n/a
AMD	CFH	rs10737680	C	A	OR (n/a CI)	genotypic	2.7	7.60
AMD	CFB-C2	rs641153	C	T	OR (n/a CI)	genotypic	9.5	3.10

FIG. 4D

Short Phenotype Name	Gene (or chr.loc on B36)	Genotypic risk: nonrisk homoz (NN vs NN)	Carrier Risk (RR or RN - vs NN)	Allelic Risk (R vs N)	Seminal publication	DIRECT or TAG SNP	Test SNP RR freq in HapMap CEU	Test SNP RN freq In HapMap CEU
AD	APOE	1	6.34 (4.76, 8.44)		Coon et al., J. Clin. Psychiatry 68:613-618 (2007)	TAG	3%	30%
BC	FGFR2	1.00			Easton et al., Nature 447:1087-1093 (2007)	DIRECT	22%	40%
BC	TNRC9	1.00			Easton et al., Nature 447:1087-1093 (2007)	DIRECT	12%	37%
BC	MAP3K1	1.00			Easton et al., Nature 447:1087-1093 (2007)	TAG	47%	45%
BC	LSP1	1.00			Easton et al., Nature 447:1087-1093 (2007)	DIRECT	8%	52%
BC	CASP8	1.00			Cox et al., Nat. Genet 39:352-358 (2007)	TAG	77%	22%
BCERP	chr2.217614077	1.00			Stacey et al., Nat. Genet. 39:865-869 (2007)	TAG	40%	45%
BCERP	TNRC9	1.00			Stacey et al., Nat. Genet. 39:865-869 (2007)	DIRECT	12%	37%
BMIOB	FTO	1.00			Frayling et al., Science 316:889-894 (2007)	DIRECT	12%	67%
BMIOW	FTO	1.00			Frayling et al., Science 316:889-894 (2007)	DIRECT	12%	67%
BP	PALB2	1.00			Wellcome Trust Case Control Consortium (WTCCC) Nature 447:661-678 (2007)	DIRECT	67%	27%
CD	chr10.101277754	1.00			Wellcome Trust Case Control Consortium (WTCCC) Nature 447:661-678 (2007)	DIRECT	30%	40%
CD	PTGER4	1.00			Wellcome Trust Case Control Consortium (WTCCC) Nature 447:661-678 (2007)	DIRECT	7%	20%
CD	ATG16L1	1.00			Wellcome Trust Case Control Consortium (WTCCC) Nature 447:661-678 (2007)	DIRECT	30%	50%
CD	BSN	1.00			Wellcome Trust Case Control Consortium (WTCCC) Nature 447:661-678 (2007)	DIRECT	3%	42%
CD	IL23R	1.00			Wellcome Trust Case Control Consortium (WTCCC) Nature 447:661-678 (2007)	DIRECT	10%	38%

FIG. 4E

Short Phenotype Name	Gene (or chr.loc on B36)	Genotypic risk: nonrisk homoz (NN vs NN)	Carrier Risk (RR or RN - vs NN)	Allelic Risk (R vs N)	Seminal publication	DIRECT or TAG SNP	Test SNP RR freq in HapMap CEU	Test SNP RN freq In HapMap CEU
CD	IRGM	1.00			Wellcome Trust Case Control Consortium (WTCCC) Nature 447:661-678 (2007)	DIRECT	0%	7%
CD	NOD2 (CARD15)	1.00			Wellcome Trust Case Control Consortium (WTCCC) Nature 447:661-678 (2007)	DIRECT	10%	52%
CD	PTPN2	1.00			Wellcome Trust Case Control Consortium (WTCCC) Nature 447:661-678 (2007)	DIRECT	5%	28%
CD	ZNF365	1.00			Wellcome Trust Case Control Consortium (WTCCC) Nature 447:661-678 (2007)	DIRECT	23%	63%
CelD	IL2-IL22 locus			1.42 (1.28-1.59)	van Heel et al., Nat. Genet. 39:827-829 (2007)	DIRECT	55%	42%
CelD	HLA-DQ2.5cis			7.04 (6.08-8.15)	van Heel Nat Genet 39:827 (2007)	DIRECT	0%	18%
CelD	CTLA4			1.24 (1.04-1.49)	Hunt et al., Eur. J. Hum. Genet. 13:440-444 (2005)	TAG	8%	58%
EMI	THBS4	1.00			Topol et al., Circulation 104:2641-6544 (2001) (main reference)	DIRECT	53%	37%
EMI	9b21	1.00			Helgadottir et al., Science 316:1491-1493 (2007): subset from McPherson et al., Science 316:1488-1491 (2007)	TAG	22%	55%
MI	9b21	1.00			Helgadottir et al., Science 316:1491-1493 (2007): subset from McPherson et al., Science 316:1488-1491 (2007)	TAG	22%	55%
OAK	GDF5	1.00			Miyamoto et al., Nat. Genet. 39:529-533 (2007)	TAG	42%	47%
PC	8q24_R1	1.00			Yeager et., Nat. Genet. 39:64-649 (2007)	TAG	0%	13%
PC	8q24_R3	1.00			Yeager et., Nat. Genet. 39:64-649 (2007)	DIRECT	18%	55%
RA	PTPN22	1.00			Wellcome Trust Case Control Consortium (WTCCC) Nature 447:661-678 (2007)	DIRECT	0%	28%
RA	MHC	1.00			Wellcome Trust Case Control Consortium (WTCCC) Nature 447:661-678 (2007)	DIRECT	22%	57%
T2D	CDKAL1	1.00			Scott et al., Science 316:1341-1345 (2007); Zeggini Science 316:1336-1341 (2007)	DIRECT	8%	45%

FIG. 4F

Short Phenotype Name	Gene (or chr.loc on B36)	Genotypic risk: nonrisk homoz (NN vs NN)	Carrier Risk (RR or RN - vs NN)	Allelic Risk (R vs N)	Seminal publication	DIRECT or TAG SNP	Test SNP RR freq in HapMap CEU	Test SNP RN freq In HapMap CEU
T2D	TCF7L2	1.00			Wellcome Trust Case Control Consortium (WTCCC) Nature 447:661-678 (2007)	DIRECT	9%	37%
T2D	CDKAL1	1.00			Steinthorsdottir et al., Nat. Genet. 39:770-775 (2007).	DIRECT	8%	33%
T2D	CDKAL1	1.00			Steinthorsdottir et al., Nat. Genet. 39:770-775 (2007).	DIRECT	8%	33%
T2D	CDKN2A/B	1.00			Scott et al., Science 316:1341-1345 (2007); Zeggini et al., Science 316:1336-1341 (2007)	DIRECT	67%	25%
T2D	Chr11.41871942	1.00			Scott et al., Science 316:1341-1345 (2007);	TAG	78%	22%
T2D	FTO	1.00			Scott et al., Science 316:1341-1345 (2007);	DIRECT	12%	67%
T2D	HHEX	1.00			Scott et al., Science 316:1341-1345 (2007);	DIRECT	32%	48%
T2D	IGF2BP2	1.00			Scott et al., Science 316:1341-1345 (2007);	DIRECT	12%	35%
T2D	KCNJ11	1.00			Scott et al., Science 316:1341-1345 (2007);	TAG	10%	62%
T2D	PPARG	1.00			Scott et al., Science 316:1341-1345 (2007);	DIRECT	87%	12%
AMD	GRK5		1.59		Jakobsdottir et al., Am. J. Hum. Genet. 77:389-407 (2005)	TAG	27%	50%
AMD	LOC387715	1.00			Maller et al., Nat. Genet. 38:1055-1059 (2006)	DIRECT	2.00%	40%
AMD	CFH	1.00			Maller et al., Nat. Genet. 38:1055-1059 (2006)	DIRECT	22%	38%
AMD	CFB-C2	1.00			Maller et al., Nat. Genet. 38:1055-1059 (2006)	TAG	0%	12%

FIG. 4G

Short Phenotype Name	Gene (or chr.loc on B36)	Test SNP-NN freq in Hap Map CEU	Test SNP-RR freq in Hap Map CHB	Test SNP-RN freq in Hap Map CHB	Test SNP-NN freq in Hap Map CHB	Test SNP RR freq in Hap Map YRI	Test SNP RN freq in Hap Map YRI	Test SNP NN freq in Hap Map YRI	Test SNP RR freq in Hap Map JAP	Test SNP RN freq in Hap Map JAP	Test SNP NN freq in Hap Map JAP
AD	APOE	67%	0%	24%	76%	2%	27%	72%	2%	13%	84%
BC	FGFR2	38%	9%	42%	49%	28%	47%	25%	4%	31%	64%
BC	TNRC9	52%	49%	44%	7%	22%	63%	15%	33%	44%	22%
BC	MAP3K1	8%	27%	42%	31%	53%	42%	5%	13%	64%	22%
BC	LSP1	40%	2%	16%	82%	0%	25%	75%	0%	29%	71%
BC	CASP8	2%	100%	0%	0%	2%	37%	62%	100%	0%	0%
BCERP	chr2.217614077	15%	0%	27%	73%	67%	27%	7%	4%	13%	82%
BCERP	TNRC9	52%	49%	44%	7%	75%	25%	0%	33%	44%	22%
BMIOB	FTO	22%	0%	24%	76%	25%	53%	22%	7%	20%	73%
BMIOW	FTO	22%	0%	24%	76%	25%	53%	22%	7%	20%	73%
BP	PALB2	7%	40%	44%	16%	5%	42%	53%	42%	49%	9%
CD	chr10.101277754	40%	31%	47%	22%	25%	48%	27%	27%	47%	27%
CD	PTGER4	73%	0%	0%	100%	0%	3%	97%	0%	0%	100%
CD	ATG16L1	20%	16%	47%	38%	8%	38%	53%	0%	33%	67%
CD	BSN	55%	0%	9%	91%				0%	16%	84%
CD	IL23R	52%	29%	49%	22%	5%	47%	48%	36%	49%	16%
CD	IRGM	93%	13%	49%	38%	7%	43%	50%	21%	39%	41%
CD	NOD2 (CARD15)	38%	0%	0%	100%	0%	0%	100%	0%	0%	100%
CD	PTPN2	67%	2%	33%	64%	28%	47%	25%	0%	16%	84%
CD	ZNF365	13%	71%	24%	4%	0%	3%	97%	49%	44%	7%
CelD	IL2-IL22 locus	3%	84%	16%	0%	82%	16%	2%	77%	21%	2%
CelD	HLA-DQ2.5cis	82%	0%	13%	87%	0%	5%	95%	0%	17%	83%

FIG. 4H

Short Phenotype Name	Gene (or chr.loc on B36)	Test SNP-NN freq in Hap Map CEU	Test SNP-RR freq in Hap Map CHB	Test SNP-RN freq in Hap Map CHB	Test SNP-NN freq in Hap Map CHB	Test SNP RR freq in Hap Map YRI	Test SNP RN freq in Hap Map YRI	Test SNP NN freq in Hap Map YRI	Test SNP RR freq in Hap Map JAP	Test SNP RN freq in Hap Map JAP	Test SNP NN freq in Hap Map JAP
CelD	CTLA4	33%	47%	42%	11%	40%	49%	11%	27%	50%	23%
EMI	THBS4	10%	96%	4%	0%	85%	15%	0%	84%	16%	0%
EMI	9p21	23%	22%	51%	27%	2%	32%	67%	27%	48%	25%
MI	9p21	23%	22%	51%	27%	2%	32%	67%	27%	48%	25%
OAK	GDF5	12%	58%	36%	7%	17%	60%	23%	51%	44%	4%
PC	8q24_R1	87%	2%	13%	84%	3%	22%	75%	4%	31%	64%
PC	8q24_R3	27%	11%	56%	33%	97%	3%	0%	11%	46%	43%
RA	PTPN22	72%	0%	0%	100%	18%	43%	38%	0%	0%	100%
RA	MHC	22%	31%	42%	27%	0%	0%	100%	30%	49%	21%
T2D	CDKAL1	47%	16%	51%	33%%	48%	37%	15%	16%	44%	40%
T2D	TCF7L2	54%	0%	4%	96%	22%	61%	17%	0%	4%	96%
T2D	CDKAL1	58%	22%	49%	29%	42%	43%	15%	23%	48%	30%
T2D	CDKAL1	58%	22%	49%	29%	42%	43%	15%	23%	48%	30%
T2D	CDKN2A/B	8%	43%	33%	24%	100%	0%	0%	29%	56%	16%
T2D	Chr11.41871942	0%	60%	33%	7%	70%	28%	2%	47%	51%	2%
T2D	FTO	22%	0%	24%	76%	23%	47%	30%	7%	20%	73%
T2D	HHEX	20%	7%	51%	42%	75%	22%	3%	21%	41%	39%
T2D	IGF2BP2	53%	4%	36%	60%	30%	50%	20%	13%	36%	51%
T2D	KCNJ11	28%	11%	49%	40%	0%	2%	98%	9%	47%	44%
T2D	PPARG	2%	96%	4%	0%	100%	0%	0%	89%	11%	0%
AMD	GRK5	23%	76%	20%	4%	82%	18%	0%	66%	21%	13%
AMD	LOC387715	58%	16%	62%	22%	8%	45%	47%	20%	47%	33%
AMD	CFH	40%	22%	42%	36%	32%	52%	17%	13%	53%	33%
AMD	CFB-C2	88%	n/a	n/a	n/a	2%	17%	81%	n/a	n/a	n/a

FIG. 4I

Short Phenotype Name	Locus	Gene (or chr.loc on B36)	Gender Applicability (F-M-B)	TEST SNP	CHR	Test Risk allele (plus, R)	Test Non Risk allele (plus, N)	Ethnicity/ Race distr	Functional or published SNP	UNITS for effect estimate
PC	PC_1 |PC_2	8q24_R1|8q24_R3	M	rs9643226|rs6983267	chr8	C|G	G|T	CEU	rs1447295|rs6983267	OR (95% CI)

Gene or chr.loc on B36	UNITS for effect estimate	2locus_ genotypic effect RRRR	2locus_ genotypic effect RRRN	2locus_ genotypic effect RRNN	2locus_ genotypic effect RNRR	2locus_ genotypic effect RNRN	2locus_ genotypic effect RNNN	Gene (or chr.loc on B36)
8q24_R1|8q24_R3	OR (95% CI)	3.17 (2.55, 3.94)	2.55 (2.10, 3.09)	2.05 (1.70, 2.46)	2.22 (1.91, 2.57)	1.78 (1.60, 1.98)	1.43 (1.30, 1.57)	8q24_R1|8q24_R3

2locus genotypic affect NNRR	2locus genotypic affect NNRN	2locus genotypic affect NNNN	Seminal publication
1.55 (1.37, 1.75)	1.24 (1.17, 1.32)	1	Yeager et, Nat. Genet. 39:64-649 (2007)

FIG. 4J

Short Phenotype Name	Locus	LOCUS_ETH	Gene (or chr.loc on B36)	Gender applicability (F, M, B)	TEST SNP	Test Risk allele (plus R)	Test NonRisk allele (plus N)	Ethnicity/Race-distr	Functional or published SNP
AMD	AMD_2_3_4	AMD_2_3_4_CEU	LOC387715|CFH|CFB-C2	B	rs10490924|rs10737680|rs541862	T|C|A	G|A|G	CEU	rs10490924|rs10737680|rs641153

CHR	UNITS for effect estimate	Effect $R_1R_1R_2R_2R_3R_3$	Effect $R_1R_1R_2R_2R_3N_3$	Effect $R_1R_1R_2R_2N_3N_3$	Effect $R_1R_1R_2N_2R_3R_3$	Effect $R_1R_1R_2N_2R_3N_3$	Effect $R_1R_1R_2N_2N_3N_3$	Effect $R_1R_1N_2N_2R_3R_3$	Effect $R_1N_1R_2R_2R_3R_3$
chr10|chr1|chrB	OR (n/a CI)	285	154	154	92.5	49.8	49.8	30	70.8

Effect $R_1R_1N_2N_2R_3N_3$	Effect $R_1R_1N_2N_2N_3N_3$	Effect $R_1N_1R_2R_2R_3N_3$	Effect $R_1N_1R_2R_2N_3N_3$	Effect $R_1N_1R_2N_2R_3R_3$	Effect $R_1N_1R_2N_2R_3N_3$	Effect $R_1N_1R_2N_2N_3N_3$	Effect $R_1N_1N_2N_2R_3R_3$	Effect $N_1N_1R_2R_2N_3N_3$	Effect $R_1N_1N_2N_2R_3N_3$
16.2	16.2	38.1	38.1	23	12.4	12.4	7.5	9.5	4

Effect $R_1N_1N_2N_2N_3N_3$	Effect $N_1N_1R_2R_2R_3R_3$	Effect $N_1N_1R_2R_2R_3N_3$	Effect $N_1N_1R_2N_2R_3R_3$	Effect $N_1N_1R_2N_2R_3N_3$	Effect $N_1N_1R_2N_2N_3N_3$	Effect $N_1N_1N_2N_2R_3N_3$	Effect $N_1N_1N_2N_2R_3N_3$	Effect $N_1N_1N_2N_2N_3N_3$	Seminal publication
4	17.6	9.5	5.7	3.1	3.1	1.9	1.9	1	Maller et al., Nat. Genet. 38:1055-1059 (2006)

FIG. 4K

Abbreviation	What Does it stand for?
CEU	European/Caucasian ethnicity
CHB	Chinese ethnicity
JAP	Japanese ethnicity
YRI	Yoruban ethnicity
R	risk allele
N	non-risk allele
CC	case control study design
Ethnicity	
C(H)	Han Chinese ethnicity
E	European
J	Japanese
L	Latine
NA-P	Native American-Pima Indians
H	Hawaiian
Af	African
As	Asian
Countries	
CH	Switzerland
Dk	Denmark
FI	Finland
GH	Ghana
IS	Iceland
IT	italy
KR	Korea
NG	Nigeria
NL	Netherlands
GB	United Kingdom
FR	France
ES	Spain
SE	Sweden
TH	Thailand
TW	Taiwan
US	United States

FIG. 4L

Short Phenotype Name	Phenotype	Heritability	Reference
AMD	Age Related Macular Degeneration	0.71[1]	Haddad et al., Survey of Opthalmology, 51:316 -363 (2006)
AD	Alzheimer's Disease	0.79[2]	Gatz et al., Arch of Gen. Psychiatry. 63:168-174 (2006)
T2D	Diabetes, Type 2	0.80	van Tilburg et al., J. Med. Genet. 38:569-578 (2001)
EMEM	Episodic Memory (Short-term)	0.50	de Quervain et al., Proc. Natl. Acad. Sci. USA 103:4270-4274 (2006).
MI	Myocardial infarction	0.57 (M), 0.38 (F)	Zdtavkovic. Karolinska Inst. 2006. http://diss.kib.ki.se/2006/91-7140-771-5/
EMI	Myocardial infarction (early onset M<45, F<50)	0.63	Roberts and Stewart, Am. Heart Hosp. J. 4:222-227 (2006)
EMI	Myocardial infarction (early onset M<50, F<60)	0.63	Roberts and Stewart, Am. Heart Hosp. J. 4:222-227 (2006)
BMIOB	Body Mass Index, obesity endpoint (BMI 30kg/m^2)	0.40	Tambs et al., Am. J. Hum. Biol. 3:257-267 (1991)
BMIOW	Body mass index, overweight endpoint (BMI>25kg/m2)	0.40	Tambs et al., Am. J. Hum. Biol. 3:257-267 (1991)
BC	Breast Cancer	0.30	Locatelli et al., Twin Res. 7:182-191 (2004).
CD	Crohn's Disease (inflammatory bowel disease)	0.58	Breslin et al., Gut 41:557-560 (1997)
BP	Bipolar Disorder	0.75	McGuffin et al., Arch. Gen. Psych. 60:497-502 (2003)
BCERP	Breast Caner, ER positive	n/a	
OAH	osteoarthritis, hip joint	0.61 (radiograph vs. self report)	Page et al., Twin Res. 6:147-151 (2003)
OAK	osteoarthritis, knee joint	0.63 (radiograph)	Zhai et al., Osteoarthritis Cartilage 15:222-225 (2007)
RA	rheumatoid arthritis	0.53	MacGregor et al., Arthritis Rheum. 2000, 43:30-37 (2000).
CelD	Celiac Disease	0.70	Nistico et al., Gut 55:803-808 (2006)
PC	Prostate Cancer	0.27	Page et al., Prostate 33:240-245 (1997)
	Colorectal cancer	0.35	Lichtenstein et al., N. Engl. J. Med. 343:78-85 (2000)

[1] MC-1-5 grade of maculopathy, her estimate for grades 4 and 5 "advanced disease", AMD

[2] Adjusted for age

FIG. 4M

Phenotype	Gene	Minor allele	Ethnicity/ Race (1)	Country (2)	Functional or published SNP	Effect estimate in homoz (3)	Effect estimate in heteroz (3)	Effect estimate in carriers (3,4)	Seminal publication
Age Related Macular Degeration	CFH	C	E	US	rs1329428	NA	NA	6.2 (2.9, 13)*	Klein et al., Science 308:385-389 (2005)
Alzheimer's Disease (conditional on carrying the APOE4 allele)	GAB2	T	E	US	rs2373115			4.06 (2.81, 14.69)* multiplied by the APOE4 risk	Reiman et al., Neuron 54:713-720 (2007)
Cardiac repolarization (QT interval)	NOS1AP	G	E	US	rs10494366		0.1±0.6**	GG: 2.7±1.0, GT:0.1±0.6, TT:-1.3±0.6**	Arking et al., Nat. Genet. 38:644-651 (2006)
Cerebral infarction	PRKCH	A	As	JP, CN	rs2230500	1.56 (1.03, 2.37)	1.28 (1.07, 1.54)	1.31 (1.11, 1.56)	Kubo et al., Nat. Genet. 39:212-217 (2007).
Crohn's Disease (inflammatory bowel disease)	IL23R	A	E	US	rs11209026			0.26 (0.15, 0.43)*	Duerr et al., Science 314:1461-1463 (2006)
Diabetes, Type 1	CTLA4	G	E	IT	rs231775			1.79 (1.20, 2.69)*	Nistico et al., Hum. Molec. Genet. 5:1075-1080 (1996)

FIG. 5A

Phenotype	Gene	Minor allele	Ethnicity/ Race (1)	Country (2)	Functional or published SNP	Effect estimate in homoz (3)	Effect estimate in heteroz (3)	Effect estimate in carriers (3,4)	Seminal publication
Diabetes, Type 2	IGF2BP2	T	E	US	rs4402960			1.18 (1.08, 1.28)*	Scott et al., Science 316:1341-1345 (2007)
Diabetes, Type 2	IGF2BP2	T		GB	rs4402960			1.11 (1.05, 1.16)*	Scott et al., Science 316:1341-1345 (2007)
Diabetes, Type 2	KCNJ11	T	E	US	rs5219			1.11 (1.02, 1.21)*	Scott et al., Science 316:1341-1345 (2007)
Diabetes, Type 2	KCNJ11	T		UK	rs5219			1.13 (1.07, 1.19)*	Scott et al., Science 316:1341-1345 (2007)
Diabetes, Type 2	SLC30A8	C	E	US	rs13266634			1.18 (1.09, 1.29)*	Scott et al., Science 316:1341-1345 (2007)
Diabetes, Type 2	SLC30A8	C		UK	rs13266634			1.12 (1.05, 1.18)*	Scott et al., Science 316:1341-1345 (2007)
Diabetes, Type 2	TCF7L2	T	E	FR	rs7903146	2.77 (2.27, 3.27)*	1.65 (1.46, 1.84)*	1.83 (1.64, 2.05)*	Sladek et al., Nature 445:881-885 (2007); Grant et al., Nat. Genet. 38:320-323 (2006)
Episodic Memory (short term)	WWC1 (KIBRA)	T	E	CH	rs1070145	NA	NA	9.4+0.2 (24% better word recall)***	Papassotiropoulos et al., Science 314:475-478 (2006)
Prostate cancer	8q24 region 1	A	E	US	rs1447295	1.42 (1.29, 1.59)*	2.23 (1.58, 3.14)*		Yeager et al., Nat Genet. 39:645-9064 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)

FIG. 5B

Phenotype	Gene	Minor allele	Ethnicity/ Race (1)	Country (2)	Functional or published SNP	Effect estimate in homoz (3)	Effect estimate in heteroz (3)	Effect estimate in carriers (3,4)	Seminal publication
Prostate cancer	8q24 region 1	A		IS	rs1447295			1.71 (1.49, 1.95)*	Gudmundsson et al., Nat. Genet. 39:631-637 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 1	A		ES	rs1447295			1.44 (1.07,1.94)*	Gudmundsson et al., Nat. Genet. 39:631-637 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 1	A		NL	rs1447295			1.39 (1.09,1.78)*	Gudmundsson et al., Nat. Genet. 39:631-637 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 1	A	A	US	rs1447295			1.25 (1.06.1.49)*	Haiman et al., Nat. Genet. 39:638-644 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 1	A	J	US	rs1447295			1.49 (1.23,1.81)*	Haiman et al., Nat. Genet. 39:638-644 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 1	A	H	US	rs1447295			2.55 (1.33,4.89)*	Haiman et al., Nat. Genet. 39:638-644 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)

FIG. 5C

Phenotype	Gene	Minor allele	Ethnicity/ Race (1)	Country (2)	Functional or published SNP	Effect estimate in homoz (3)	Effect estimate in heteroz (3)	Effect estimate in carriers (3,4)	Seminal publication
Prostate cancer	8q24 region 1	A	L	US	rs1447295			1.98 (1.49,2.61)*	Haiman et al., Nat. Genet. 39:638-644 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 2/HapC	A	E	US	rs16901979			1.44 (1.21, 1.70)*	Gudmundsson et al., Nat. Genet. 39:631-637 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 2/HapC	A	E	IS	rs16901979			2.08 (1.66, 2.60)*	Gudmundsson et al., Nat. Genet. 39:631-637 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 2/HapC	A	E	ES	rs16901979			2.13 (1.34, 3.40)*	Gudmundsson et al., Nat. Genet. 39:631-637 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 2/HapC	A	E	NL	rs16901979			1.85 (1.05, 3.27)*	Gudmundsson et al., Nat. Genet. 39:631-637 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 2/HapC	A	A	US	rs16901979			1.34 (1.18, 1.53)*	Haiman et al., Nat. Genet. 39:638-644 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)

FIG. 5D

Phenotype	Gene	Minor allele	Ethnicity/ Race (1)	Country (2)	Functional or published SNP	Effect estimate in homoz (3)	Effect estimate in heteroz (3)	Effect estimate in carriers (3,4)	Seminal publication
Prostate cancer	8q24 region 2/HapC	A	J	US	rs16901979			1.78 (1.47, 2.15)*	Haiman et al., Nat. Genet. 39:638-644 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 2/HapC	A	H	US	rs16901979			3.17 (1.87, 5.36)*	Haiman et al., Nat. Genet. 39:638-644 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 2/HapC	A	L	US	rs16901979			1.99 (1.34, 2.96)*	Haiman et al., Nat. Genet. 39:638-644 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 3	G	E	US	rs6983267	1.26 (1.13, 1.41)*	1.58 (1.40, 1.78)*		Yeager et al., Nat Genet. 39:645-9064 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 3	G	A	US	rs6983267			1.33 (1.17, 1.75)*	Haiman et al., Nat. Genet. 39:638-644 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 3	G	J	US	rs6983267			1.23 (1.04, 2.46)*	Haiman et al., Nat. Genet. 39:638-644 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Prostate cancer	8q24 region 3	G	H	US	rs6983267			1.38 (0.89, 2.14)*	Haiman et al., Nat. Genet. 39:638-644 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)

FIG. 5E

Phenotype	Gene	Minor allele	Ethnicity/ Race (1)	Country (2)	Functional or published SNP	Effect estimate in homoz (3)	Effect estimate in heteroz (3)	Effect estimate in carriers (3,4)	Seminal publication
Prostate cancer	8q24 region 3	G	L	US	rs6983267			1.29 (1.07, 1.56)*	Haiman et al., Nat. Genet. 39:638-644 (2007); meta-analysis Witte et al., Nat. Genet. 39:579-580 (2007)
Rheumatoid arthritis	PTPN22	T	E	US	rs2476601	2.26 (0.56, 9.14)*	1.69 (1.23, 2.32)*	1.71 (1.25, 2.34)*	Begovich et al., Am. J. Hum. Genet. 75:330-337 (2004)

FIG. 5F

Phenotype	Gene	Direct or Tag SNP	Covered by	r2 (single or multi)	Risk Haplo/Diplotypes (Tag GT = Risk GT)	Other allele	Remarks
Age Related Macular Degeration	CFH	Tag	rs10737680	1	AA=CC; AC=CT; CC=TT	T	3.68% PP; 30%PP of >75 yo; 0.07% PI; other possible identifiers: haplotype Y402H, rs 1061170
Alzheimer's Disease (conditional on carrying the APOE4 allele)	GAB2	Direct				G	
Cardiac repolarization (QT interval)	NOS1AP	Tag	rs12733821	1	GG=GG; GC=GT; CC=TT	T	
Cerebral infarction	PRKCH	Tag					
Crohn's Disease (inflammatory bowel disease)	IL23R	Direct				G	0.18% population prevalence
Diabetes, Type 1	CTLA4	Direct				A	0.12% PP(5); 0.01% PI(6)
Diabetes, Type 2	IGF2BP2	Direct				G	
Diabetes, Type 2	IGF2BP2	Direct				G	
Diabetes, Type 2	KCNJ11					T	
Diabetes, Type 2	KCNJ11					T	

FIG. 5G

Phenotype	Gene	Direct or Tag SNP	Covered by	r2 (single or multi)	Risk Haplo/Diplotypes (Tag GT = Risk GT)	Other allele	Remarks
Diabetes, Type 2	SLC30A8					C	
Diabetes, Type 2	SLC30A8					C	
Diabetes, Type 2	TCF7L2	Tag	rs4506565	0.92	TT=TT (9.1%); TA=TC (35.2%); AA=CC (52.3%);// TA=CC (2.3%); TT=CT (1.1%)	C	(ii); 5.88%PP; 0.29%PI; other possible identifiers: haplotype DG10S478, rs12255372
Episodic Memory (short term)	WWC1 (KIBRA)	Direct				C	>45 avg age of onset
Prostate cancer	8q24 region 1	Tag	rs9643226	1.000		C	9% PAR (7)
Prostate cancer	8q24 region 1	Tag	rs9643226	1.000	GG=CC; GC=CA; CC=AA	C	
Prostate cancer	8q24 region 1	Tag	rs9643226	1.000	GG=CC; GC=CA; CC=AA	C	
Prostate cancer	8q24 region 1	Tag	rs9643226	1.000	GG=CC; GC=CA; CC=AA	C	
Prostate cancer	8q24 region 1	Tag	rs9643226	1.000	GG=CC; GC=CA; CC=AA	C	
Prostate cancer	8q24 region 1	Tag	rs9643226	1.000	GG=CC; GC=CA; CC=AA	C	
Prostate cancer	8q24 region 1	Tag	rs9643226	1.000	GG=CC; GC=CA; CC=AA	C	
Prostate cancer	8q24 region 1	Tag	rs9643226	1.000	GG=CC; GC=CA; CC=AA	C	
Prostate cancer	8q24 region 2/HapC	Direct				C	

FIG. 5H

Phenotype	Gene	Direct or Tag SNP	Covered by	r2 (single or multi)	Risk Haplo/Diplotypes (Tag GT = Risk GT)	Other allele	Remarks
Prostate cancer	8q24 region 2/HapC	Direct				C	
Prostate cancer	8q24 region 2/HapC	Direct				C	
Prostate cancer	8q24 region 2/HapC	Direct				C	
Prostate cancer	8q24 region 2/HapC	Direct				C	
Prostate cancer	8q24 region 2/HapC	Direct				C	
Prostate cancer	8q24 region 2/HapC	Direct				C	
Prostate cancer	8q24 region 2/HapC	Direct				C	
Prostate cancer	8q24 region 3	Tag	rs10505477	0.935	TT=GG; TC=GT; CC=TT	T	21% PAR
Prostate cancer	8q24 region 3	Tag	rs10505477	0.935	TT=GG; TC=GT; CC=TT	T	
Prostate cancer	8q24 region 3	Tag	rs10505477	0.935	TT=GG; TC=GT; CC=TT	T	
Prostate cancer	8q24 region 3	Tag	rs10505477	0.935	TT=GG; TC=GT; CC=TT	T	
Prostate cancer	8q24 region 3	Tag	rs10505477	0.935	TT=GG; TC=GT; CC=TT	T	

FIG. 5I

Phenotype	Gene	Direct or Tag SNP	Covered by	r2 (single or multi)	Risk Haplo/Diplotypes (Tag GT = Risk GT)	Other allele	Remarks
Rheumatoid arthritis	PTPN22	Tag	rs6679677		AA=TT; AC=TC; CC=CC	C	1% PP

Notes:

(1) Ancestry: C(H)=Han Chinese, E=European, J=Japanese, L=Latino, H=Hawaiian, A=African

(2) DK=Denmark, FI=Finland, GH=Ghana, IS=Iceland, IT=Italy, NG=Nigeria, NL=Netherlands, GB=United Kingdom, FR=France, ES=Spain, SE=Sweden, CH=Switzerland, US=United States.

(3) Due to the different study designs, effect estimates are reported as follows:

*Odds ratio (95% confidence interval).

**Difference from mean+/-standard error for each genotype level.

***Mean+/-standard error

****Hazard ratio (95% confidence interval). An overall effect estimate is reported if multiple populations are reported in the cited publication, when available.

Effect estimates adjusted for covariates are reported, when available.

(4) Carriers=Homozygotes + heterozygotes

(5) PP=population prevalence (USA=300M)

(6) PI=population incidence (USA)

(7) PAR=population attributable risk

FIG. 5J

Phenotype	Gene	Haplotype	Identifying SNPs	Average age of onset	Population Prevalence (USA = 300M people	Population Incidence (USA)	No. copies of at-risk allele (% of population)	Estimated Relative Risk. Increase (het)	Modified age of onset (het)
Alcoholism	ALDH2	GLU504LYS	rs671	>30	5.55% (16.65M)				
Alzheimer's Disease	ApoE	ApoE-e4	rs11083750	>65	1.47% (4M) will rise to 5% (16M) by 2050: 50% at 85		73%	0.5-1.0	84
Breast Cancer	BRCA2	N372H	rs144848		0.08% (240k)	0.08% (240k)			
Celiac Disease	HLA-DQA1	201	rs4988889(T)+rs2858331(T)		0.4% (1.2M)				
Colon Cancer	APC	I1307K	rs28933380		0.05% (150k)	0.035% (106k/yr)			
coronary heart disease	eNOS		rs1799983						
coronary heart disease	MTHFR		rs1801133						
coronary heart disease	APOB	Ins/Del/Sp1/EcoR1							
Creutzfeld-Jakob	PRNP	M129V	rs1799990		0% (20)	0% (20/yr)			
Crohn's Disease (inflammatory bowel disease)	CARD15	n/a	rs2066845 & rs2066844		0.18% (540k)				
Cystic Fibrosis	CFTR	deltaF508	various		0.01% (30k)	0.009% (2.5k)			

FIG. 6A

Phenotype	Gene	Haplotype	Identifying SNPs	Average age of onset	Population Prevalence (USA = 300M people	Population Incidence (USA)	No. copies of at-risk allele (% of population)	Estimated Relative Risk. Increase (het)	Modified age of onset (het)
Diabetes Type 1	HLA-DR	DRB1*0301	rs2040410		0.12% (360k)	0.01% (30k/yr)			
Diabetes Type 1	HLA-DQ	Multiple Haplotypes (protective/not)	various		0.12% (360k)	0.01% (30k/yr)			
Diabetes Type 1	INS	class 1 VNTR	n/a		0.12% (360k)	0.01% (30k/yr)			
Diabetes Type 1	CTLA4		rs231775		0.12% (360k)	0.01% (30k/yr)			
Diabetes Type 1	PTPN22	R620W	rs2476601		0.12% (360k)	0.01% (30k/yr)			
Diabetes Type 1	IFIH1	A946T	rs1990760		0.12% (360k)	0.01% (30k/yr)			
Episodic Memory	CAMTA1		rs4908449						
Lupus	IRF5		rs2004640		0.51% (1.53M)				
Multiple Sclerosis	HLA-DRB	B801/DRB1/0301/DQA1/0501	rs319763© +rs 4639334©		1.12% (3.6M)				
Multiple Sclerosis	HLA-DQA1	102	rs9268428© +r s6457594(a)+ RS7451962©		0.14% (420k)				
Multiple Sclerosis	HLA-DRB	drb1	RS3135388		0.14% (420k)				

FIG. 6B

Phenotype	Gene	Haplotype	Identifying SNPs	Average age of onset	Population Prevalence (USA = 300M people	Population Incidence (USA)	No. coples of at-risk allele 1% of population)	Estimation Relative Risk. Increase (het)	Modified age of onset (het)
Osteoporosis	COL1A1	Sp1	rs1800012		10.29% (30.87M)				
Progressive supra-nuclear palsy	MAPT	H1	various	60	0.01% (30k)	0.004% (12k)			
Protective against Alzheimer's Disease	ApoE	ApoE-e2		>65	1.47% (4M) will rise to 5% (16M) by 2050; 50% at 85			1.0-24.0	
Protective against HIV infection	CCR5	d32	n/a	>14	0.33% (990k)	0.01% (30k)			
Psoriasis	HLA-C	602	rs887466(G)+ rs4379333©		2.02% (6.06M)				
Rheumatoid arthritis	HLA-DRB	DRB1	various		1% (3M)				
Schizophrenia	DRD3	SER9GLY	rs6280		0.81% (2.43M)				
Systemic Lupus SLE	HLA-DRB1	1501	rs3135388		0.51% (1.53M)				
Thrombosis	factor V Leiden	R506Q	rs6025	>50	0.1% (300k)	0.1% (300k)	96%	1	>50

FIG. 6C

Phenotype	Gene	heterozygous for at-risk allele (% of population)	Estimated relative risk Increase (het)	Modified age of onset (het)	homozygous for at-risk allele (% of population)	Estimated relative risk Increase (homo)	Modified age of onset (homo)	Seminal Publication
Alcoholism	ALDH2		0.2					Yoshida et al., Am. J. Hum. Genet. 35:1107-1116 (1983)
Alzheimer's Disease	ApoE	24%	3.0-5.0	75	3%	24	68	Corder et al., Science 261:921-923 (1993)
Breast Cancer	BRCA2		1.3					Healey et al., Nat. Genet. 26:362-364 (2000)
Celiac Disease	HLA-DQA1		7					Greco et al., Gut 50:624-628 (2002)
Colon Cancer	APC		2					Laken et al., Nat. Genet. 17:79-83 (1997)
coronary heart disease	eNOS							Casas et al., Circulation 109:1359-1365 (2004)
coronary heart disease	MTHFR							
coronary heart disease	APOB							
Creutzfeld-Jakob	PRNP		0.65					Doh-ura et al., Biochem. Biophys. Res. Commun. 163:974-979 (1989)
Crohn's Disease (inflammatory bowel disease)	CARD15		3-5					Hugot et al., Nature 411:559-603 (2001)
Cystic Fibrosis	CFTR							
Diabetes Type 1	HLA-DR		4-5					Dunsworth et al., Clin. Genet. 21:233-236 (1982)

FIG. 6D

Phenotype	Gene	heterozygous for at-risk allele (% of population)	Estimated relative risk Increase (het)	Modified age of onset (het)	homozygous for at-risk allele (% of population)	Estimated relative risk Increase (homo)	Modified age of onset (homo)	Seminal Publication
Diabetes Type 1	HLA-DQ		n/a					Greenbaum et al. J. Clin. Endocr. Metab. 85:1255-1260 (2000)
Diabetes Type 1	INS		1.5-2					Pugliese et al., Nature 15:293-297 (1997)
Diabetes Type 1	CTLA4		1.4-15					Nistico et al., Hum. Molec. Genet. 5:1075-1080 (1996)
Diabetes Type 1	PTPN22		1.7					Bottini et al., Nat. Genet. 36:337-338 (2004)
Diabetes Type 1	IFIH1		0.8					Smyth et al., Nat. Genet. 38:617-619 (2006)
Episodic Memory	CAMTA1							
Lupus	IRF5		1.8					Graham et al., Nat. Genet. 38:550-555 (2006)
Multiple Sclerosis	HLA-DRB		2.5					Heward et al., J. Clin. Endocr. Metab. 83:3394-3397 (1998)
Multiple Sclerosis	HLA-DQA1		4					Fernandez-Arquero et al., Neurology 53:1361-1363 (1999)
Multiple Sclerosis	HLA-DRB		4					Gregersen et al., Nature 443:574-577 (2006)

FIG. 6E

Phenotype	Gene	heterozygous for at-risk allele (% of population)	Estimated relative risk Increase (het)	Modified age of onset (het)	homozygous for at-risk allele (% of population)	Estimated relative risk Increase (homo)	Modified age of onset (homo)	Seminal Publication
Osteoporosis	COL1A1		1.6					Grant et al., Nat. Genet. 14:203-205 (1996)
Progressive supra-nuclear palsy	MAPT		3.5					Baker et al., Hum. Molec. Genet. 8:711-715 (1999)
Protective against Alzheimer's Disease	ApoE		0.6-3		1%	0.5	>84	Farrer et al., JAMA 278:1349-1356 (1997)
Protective against HIV infection	CCR5		n/a					Samson et al., Nature 382:722-725 (1996)
Psoriasis	HLA-C		5					Walsh et al., Am. J. Hum. Genet. 73:580-590 (2003)
Rheumatoid arthritis	HLA-DRB		2-4					Michou et al., Arthritis Res. Ther. 8(:R79 (2006)
Schizophrenia	DRD3		1.7					Crocq et al., J. Med. Genet. 29:858-860 (1992)
Systemic Lupus SLE	HLA-DRB1		4.5					Green et al., Ann. Hum. Genet. 50:93-96 (1986)
Thrombosis	factor V Leiden	3%	7	<50	<1%	80	<50	Bertina et al., Nature 369:64-67 (1994)

FIG. 6F

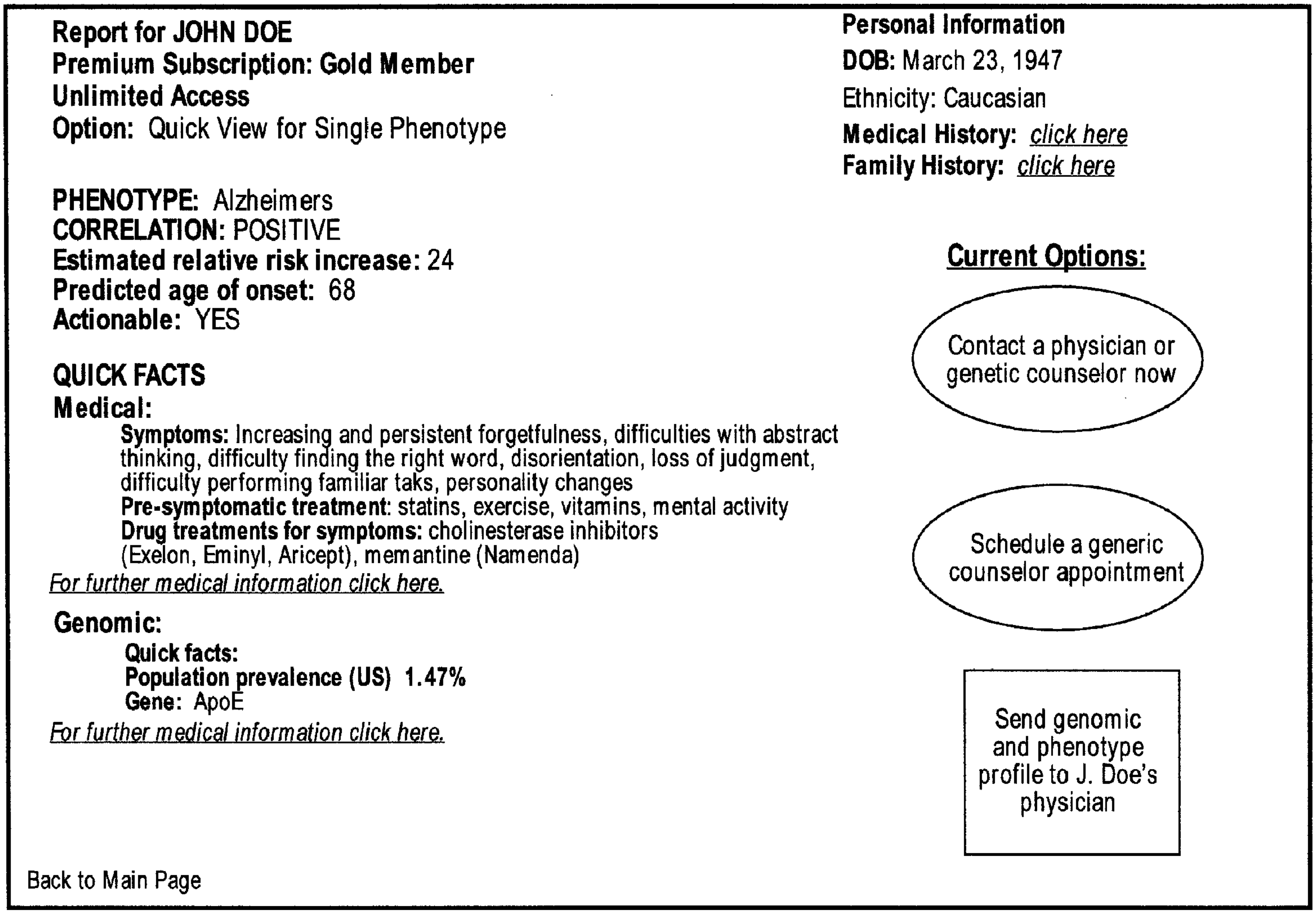

Report for JOHN DOE
Premium Subscription: Gold Member
Unlimited Access
Option: Quick View for Single Phenotype
PHENOTYPE: Alzheimers
CORRELATION: POSITIVE
Estimated relative risk increase: 24
Predicted age of onset: 68
Actionable: YES
QUICK FACTS
Medical:
Symptoms: Increasing and persistent forgetfulness, difficulties with abstract thinking, difficulty finding the right word, disorientation, loss of judgment, difficulty performing familiar taks, personality changes
Pre-symptomatic treatment: statins, exercise, vitamins, mental activity
Drug treatments for symptoms: cholinesterase inhibitors (Exelon, Eminyl, Aricept), memantine (Namenda)
For further medical information click here.
Genomic:
Quick facts:
Population prevalence (US) 1.47%
Gene: ApoE
For further medical information click here.
Back to Main Page
Personal Information
DOB: March 23, 1947
Ethnicity: Caucasian
Medical History: click here
Family History: click here
Current Options:
Contact a physician or genetic counselor now
Schedule a generic counselor appointment
Send genomic and phenotype profile to J. Doe's physician

FIG. 7

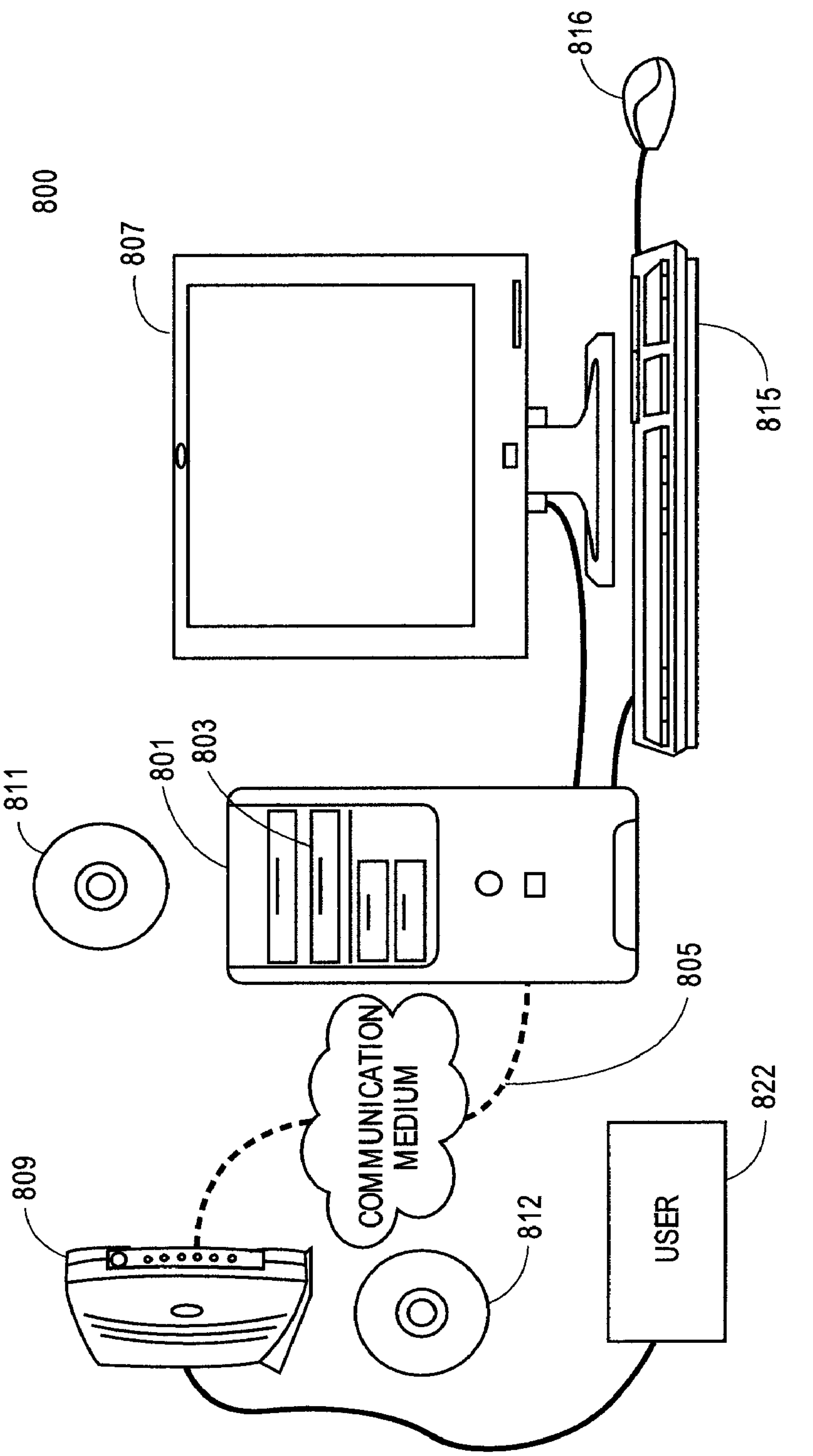

800
807
816
815
811
801
803
805
809
COMMUNICATION MEDIUM
812
822
USER

FIG. 8

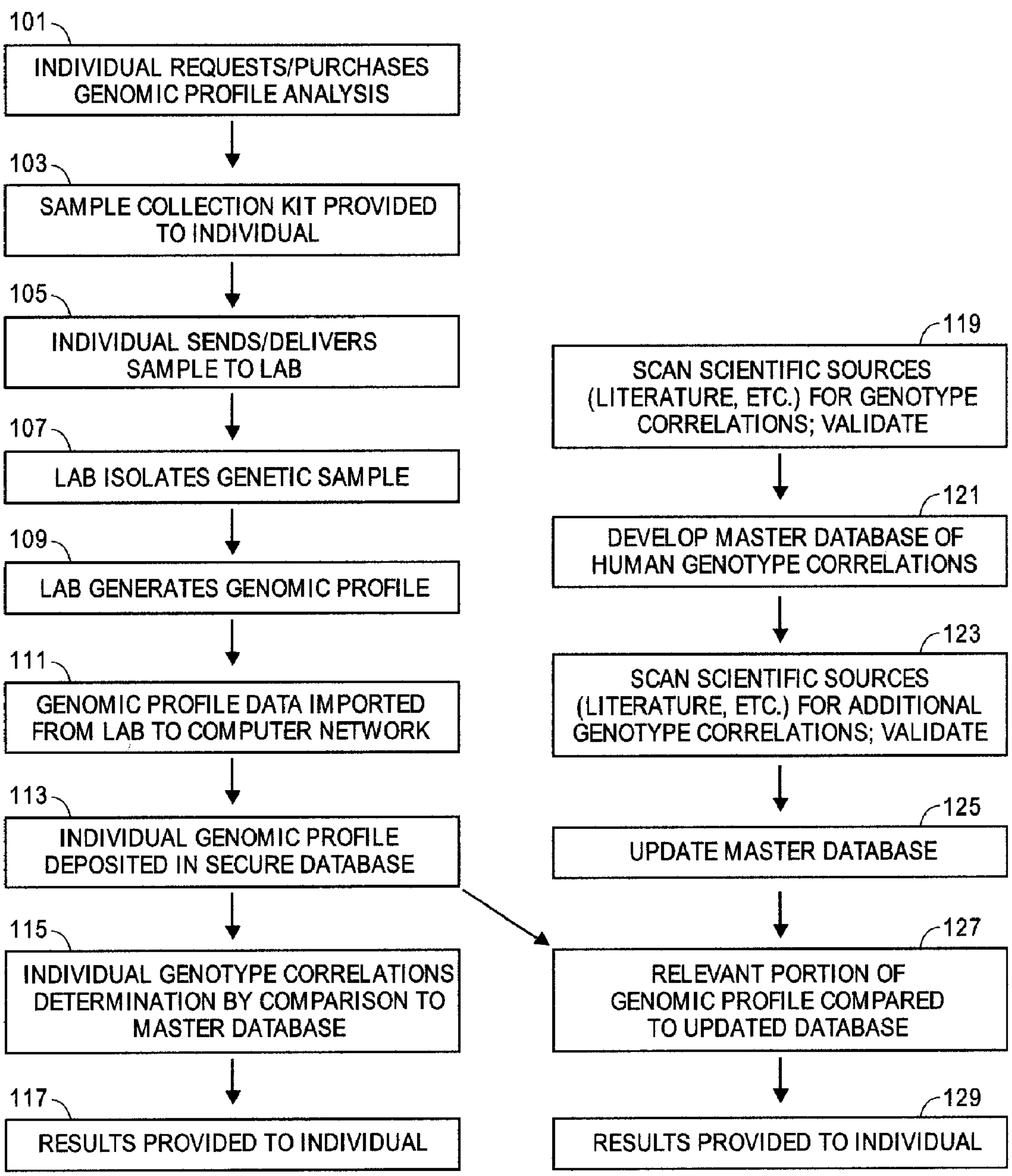

101
INDIVIDUAL REQUESTS/PURCHASES GENOMIC PROFILE ANALYSIS
103
SAMPLE COLLECTION KIT PROVIDED TO INDIVIDUAL
105
INDIVIDUAL SENDS/DELIVERS SAMPLE TO LAB
107
LAB ISOLATES GENETIC SAMPLE
109
LAB GENERATES GENOMIC PROFILE
111
GENOMIC PROFILE DATA IMPORTED FROM LAB TO COMPUTER NETWORK
113
INDIVIDUAL GENOMIC PROFILE DEPOSITED IN SECURE DATABASE
115
INDIVIDUAL GENOTYPE CORRELATIONS DETERMINATION BY COMPARISON TO MASTER DATABASE
117
RESULTS PROVIDED TO INDIVIDUAL
119
SCAN SCIENTIFIC SOURCES (LITERATURE, ETC.) FOR GENOTYPE CORRELATIONS; VALIDATE
121
DEVELOP MASTER DATABASE OF HUMAN GENOTYPE CORRELATIONS
123
SCAN SCIENTIFIC SOURCES (LITERATURE, ETC.) FOR ADDITIONAL GENOTYPE CORRELATIONS; VALIDATE
125
UPDATE MASTER DATABASE
127
RELEVANT PORTION OF GENOMIC PROFILE COMPARED TO UPDATED DATABASE
129
RESULTS PROVIDED TO INDIVIDUAL

FIG. 9

FIG. 10

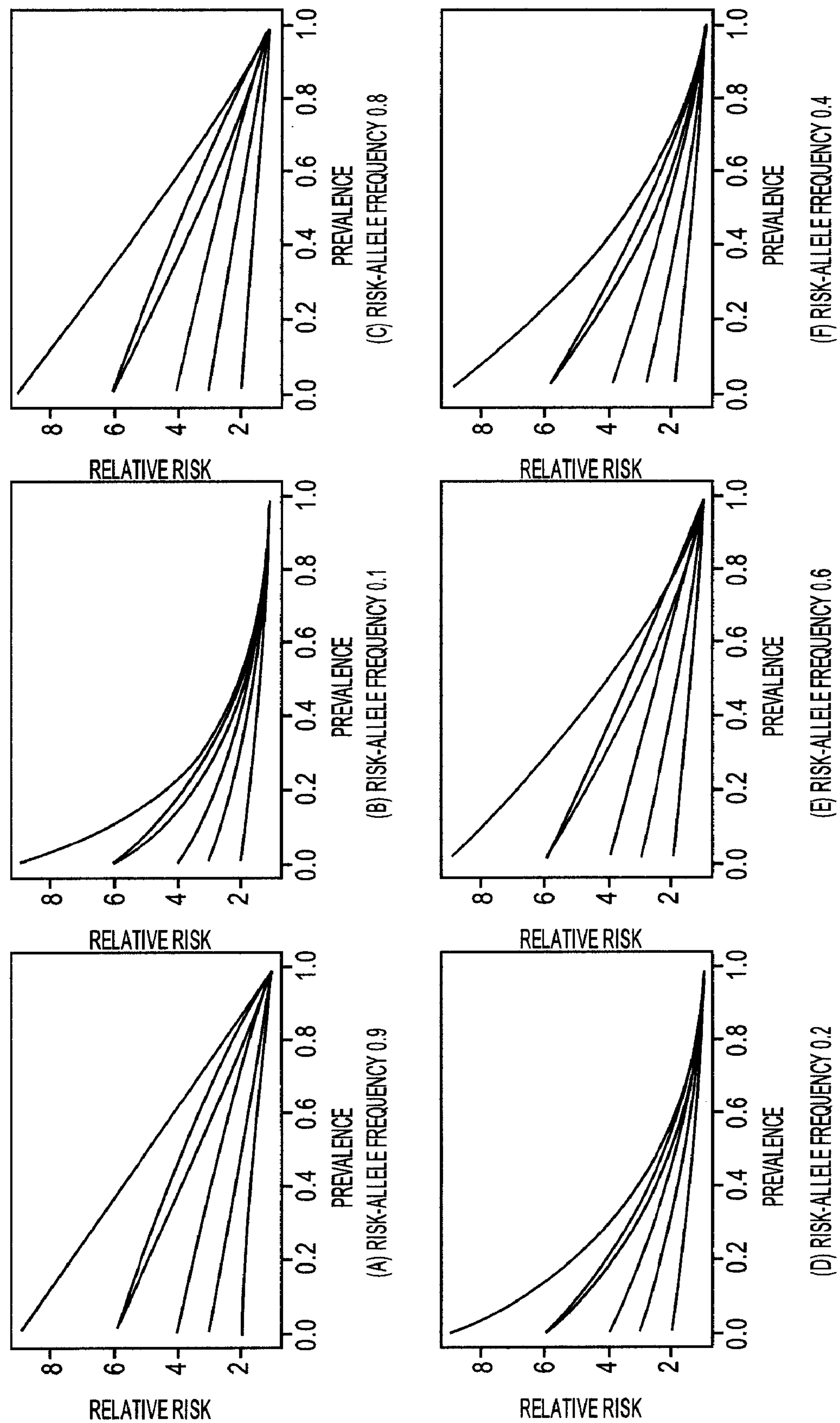

RELATIVE RISK
PREVALENCE
(A) RISK-ALLELE FREQUENCY 0.9
(B) RISK-ALLELE FREQUENCY 0.1
(C) RISK-ALLELE FREQUENCY 0.8
(D) RISK-ALLELE FREQUENCY 0.2
(E) RISK-ALLELE FREQUENCY 0.6
(F) RISK-ALLELE FREQUENCY 0.4

FIG. 11

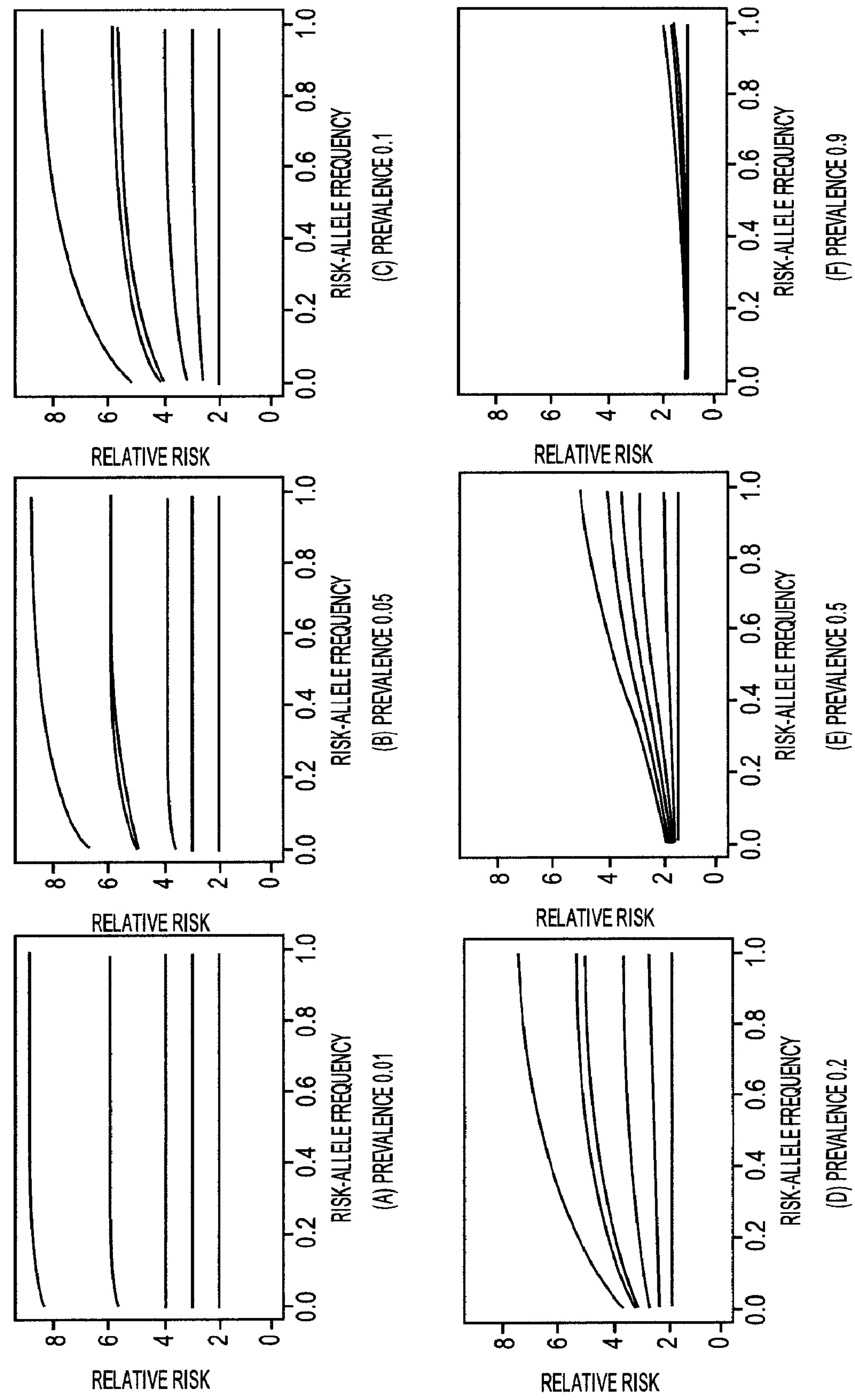

RELATIVE RISK
RISK-ALLELE FREQUENCY
(A) PREVALENCE 0.01
(B) PREVALENCE 0.05
(C) PREVALENCE 0.1
(D) PREVALENCE 0.2
(E) PREVALENCE 0.5
(F) PREVALENCE 0.9

FIG. 12

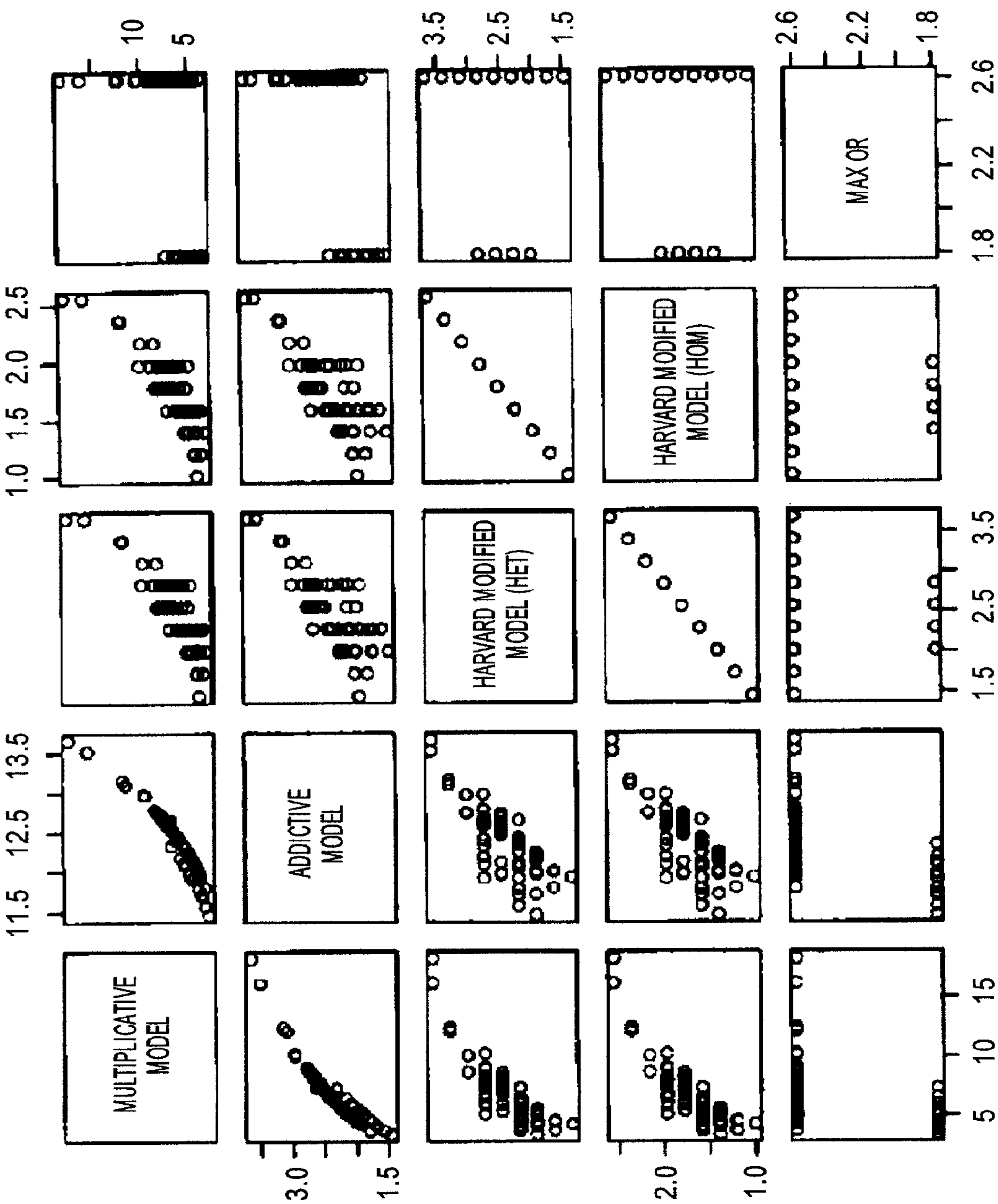

MULTIPLICATIVE MODEL
ADDICTIVE MODEL
HARVARD MODIFIED MODEL (HET)
HARVARD MODIFIED MODEL (HOM)
MAX OR

FIG. 13

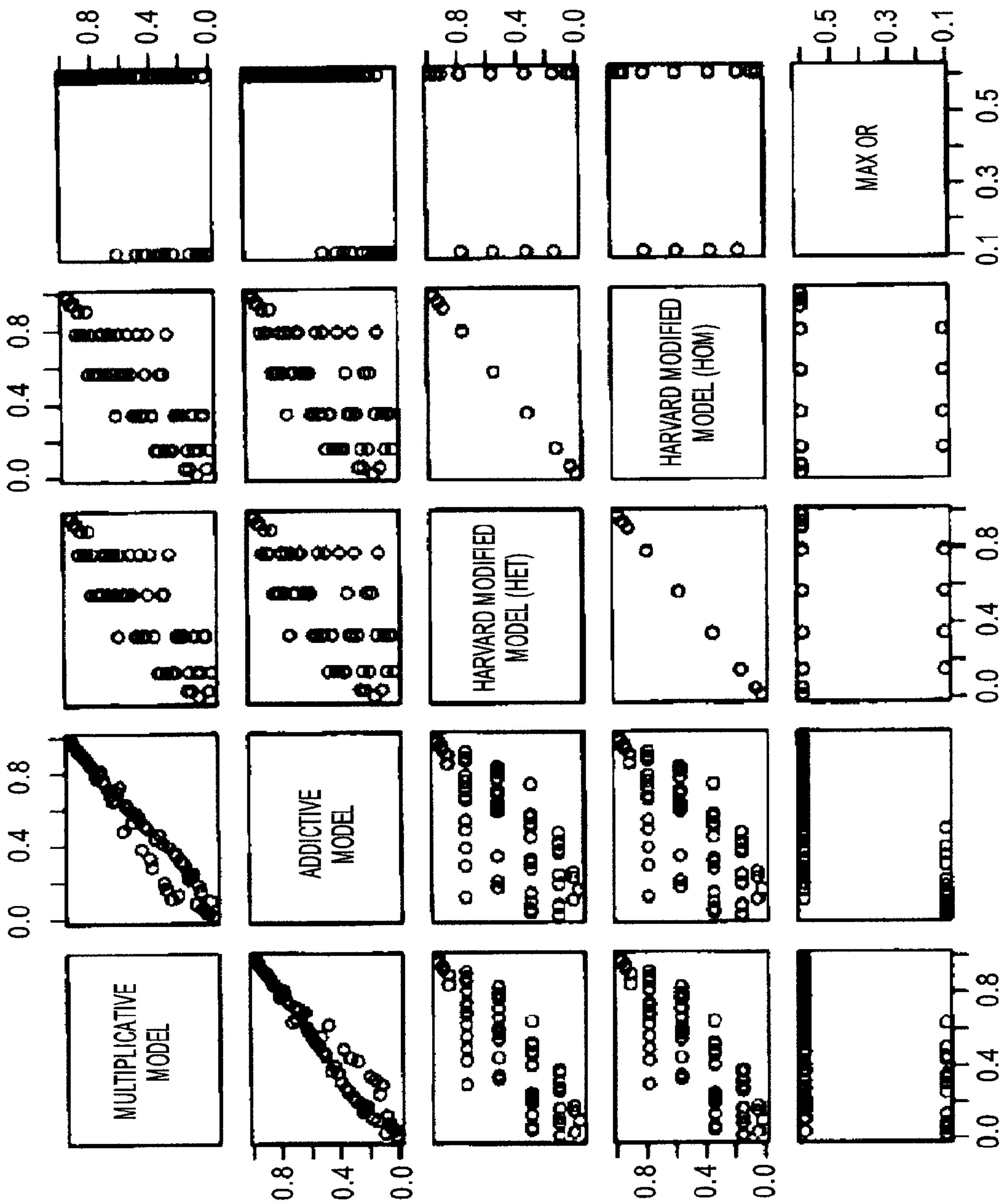

MULTIPLICATIVE MODEL
ADDICTIVE MODEL
HARVARD MODIFIED MODEL (HET)
HARVARD MODIFIED MODEL (HOM)
MAX OR

FIG. 14

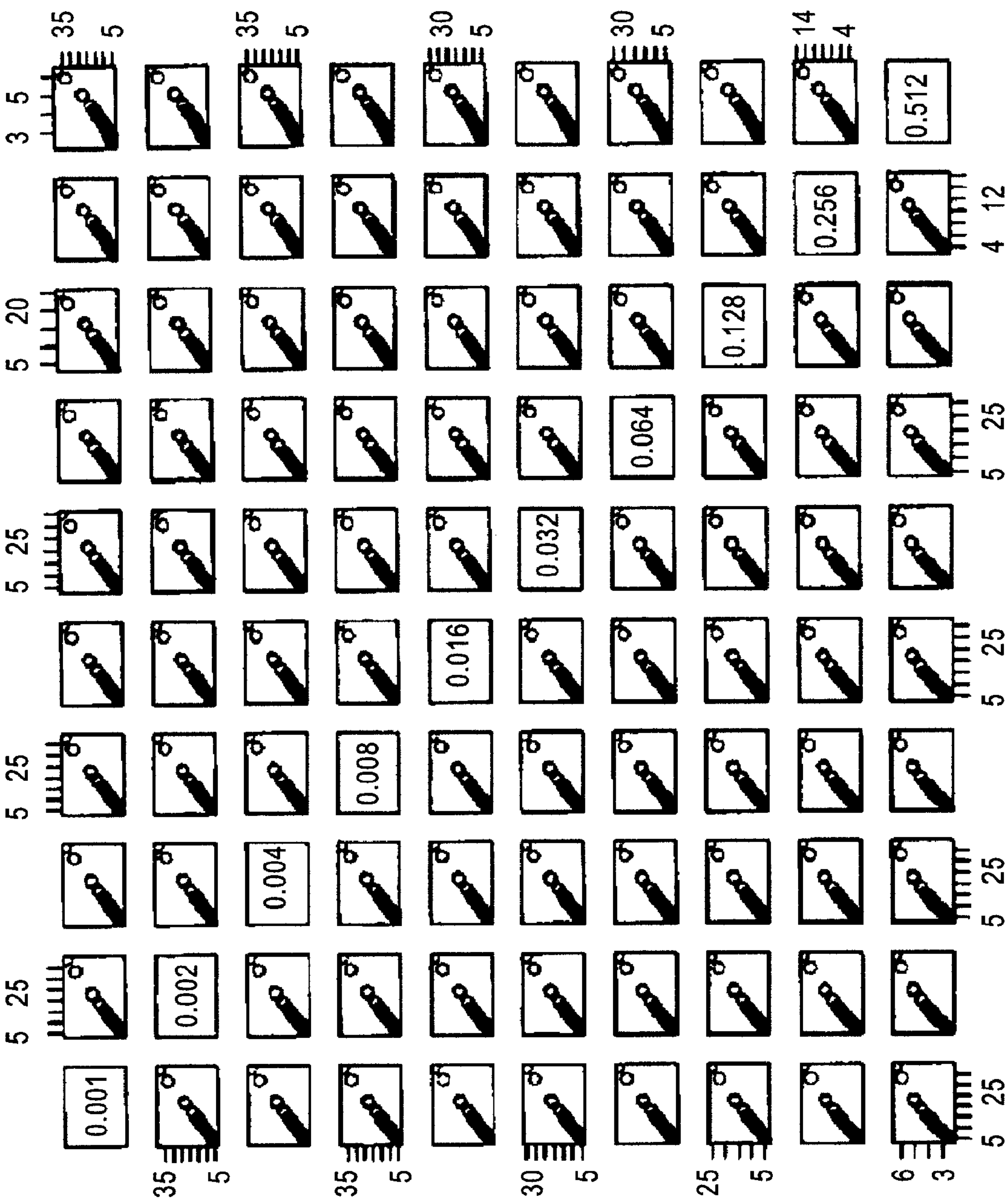


FIG. 15A

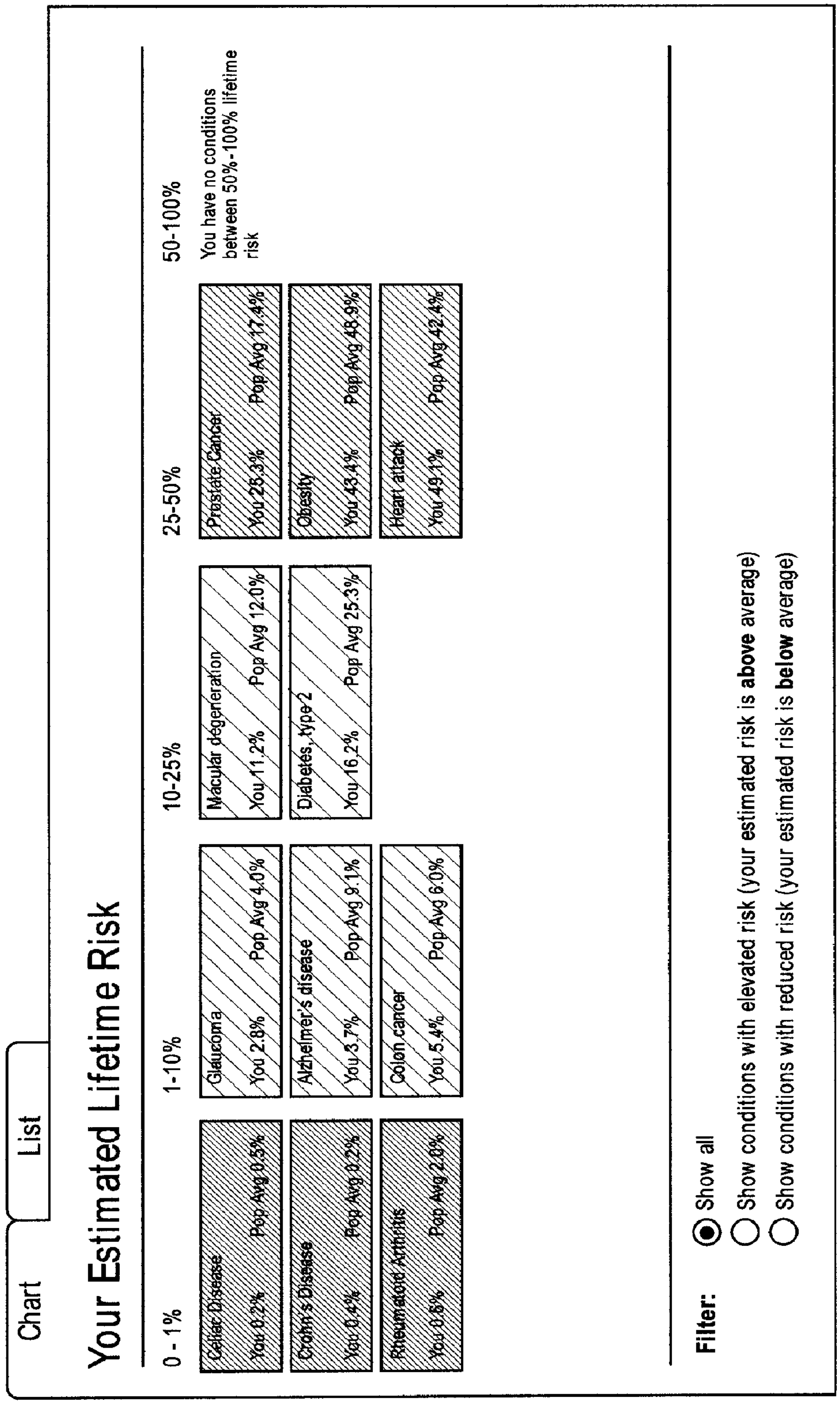


Chart
List
Your Estimated Lifetime Risk
0 - 1%
Celiac Disease
You 0.2% Pop Avg 0.5%
Crohn's Disease
You 0.4% Pop Avg 3.2%
Rheumatoid Arthritis
You 0.6% Pop Avg 2.0%
1-10%
Glaucoma
You 2.8% Pop Avg 4.0%
Alzheimer's disease
You 3.7% Pop Avg 9.1%
Colon cancer
You 5.4% Pop Avg 6.0%
10-25%
Macular degeneration
You 11.2% Pop Avg 12.0%
Diabetes, type 2
You 16.2% Pop Avg 25.3%
25-50%
Prostate Cancer
You 28.3% Pop Avg 17.4%
Obesity
You 43.4% Pop Avg 48.9%
Heart attack
You 49.1% Pop Avg 42.4%
50-100%
You have no conditions between 50%-100% lifetime risk
Filter:
Show all
Show conditions with elevated risk (your estimated risk is **above** average)
Show conditions with reduced risk (your estimated risk is **below** average)

FIG. 15B

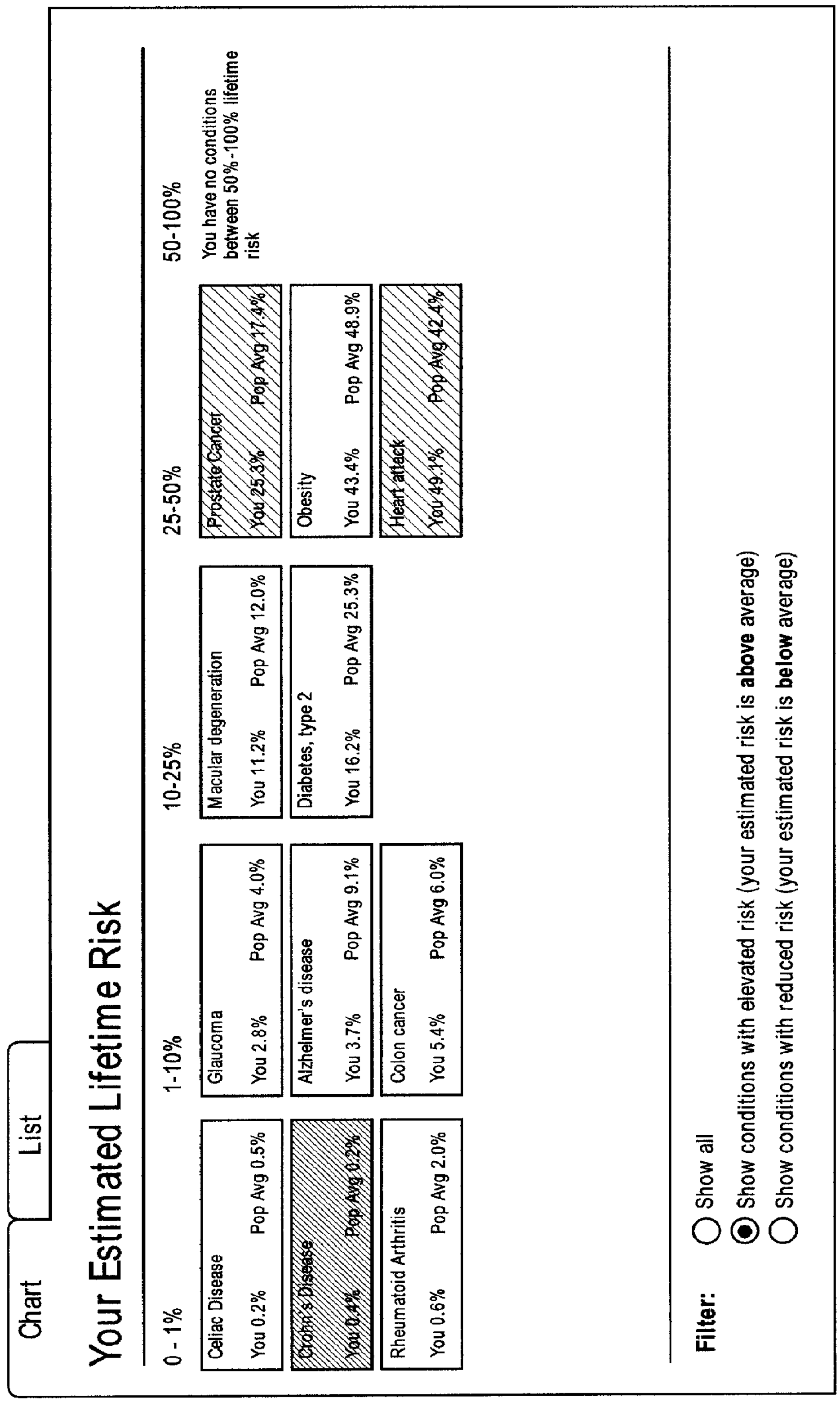


Chart
List
Your Estimated Lifetime Risk
0 - 1%
1-10%
10-25%
25-50%
50-100%
Celiac Disease
You 0.2% Pop Avg 0.5%
Crohn's Disease
You 0.4% Pop Avg 0.2%
Rheumatoid Arthritis
You 0.6% Pop Avg 2.0%
Glaucoma
You 2.8% Pop Avg 4.0%
Alzheimer's disease
You 3.7% Pop Avg 9.1%
Colon cancer
You 5.4% Pop Avg 6.0%
Macular degeneration
You 11.2% Pop Avg 12.0%
Diabetes, type 2
You 16.2% Pop Avg 25.3%
Prostate Cancer
You 25.3% Pop Avg 17.4%
Obesity
You 43.4% Pop Avg 48.9%
Heart attack
You 49.1% Pop Avg 42.4%
You have no conditions between 50%-100% lifetime risk
Filter:
Show all
Show conditions with elevated risk (your estimated risk is **above** average)
Show conditions with reduced risk (your estimated risk is **below** average)

FIG. 15C

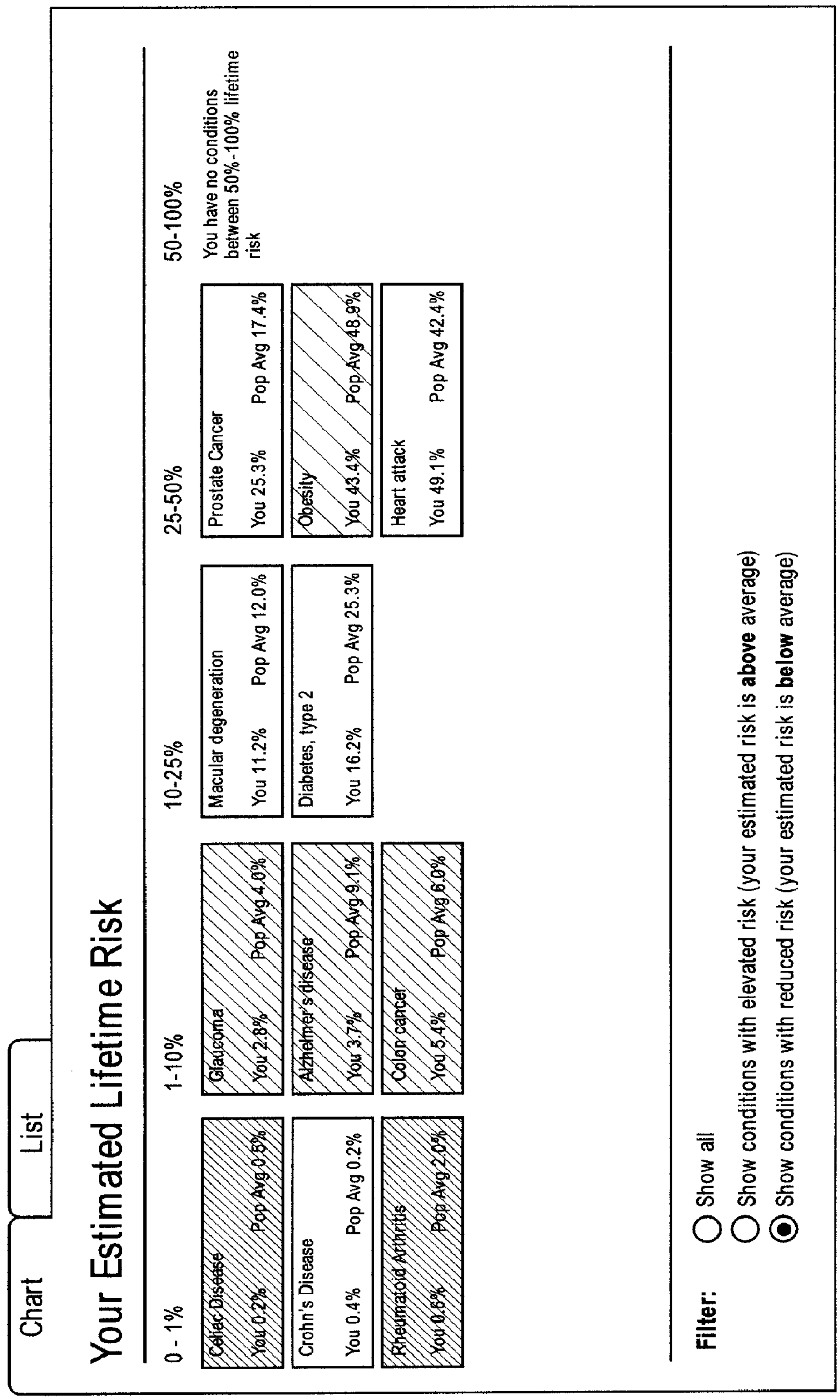


Chart
List
Your Estimated Lifetime Risk
0 - 1%
1-10%
10-25%
25-50%
50-100%
Celiac Disease
You 0.2% Pop Avg 0.5%
Crohn's Disease
You 0.4% Pop Avg 0.2%
Rheumatoid Arthritis
You 0.6% Pop Avg 2.0%
Glaucoma
You 2.8% Pop Avg 4.0%
Alzheimer's disease
You 3.7% Pop Avg 9.1%
Colon cancer
You 5.4% Pop Avg 6.0%
Macular degeneration
You 11.2% Pop Avg 12.0%
Diabetes, type 2
You 16.2% Pop Avg 25.3%
Prostate Cancer
You 25.3% Pop Avg 17.4%
Obesity
You 43.4% Pop Avg 48.9%
Heart attack
You 49.1% Pop Avg 42.4%
You have no conditions between 50%-100% lifetime risk
Filter:
Show all
Show conditions with elevated risk (your estimated risk is above average)
Show conditions with reduced risk (your estimated risk is below average)

FIG. 15D

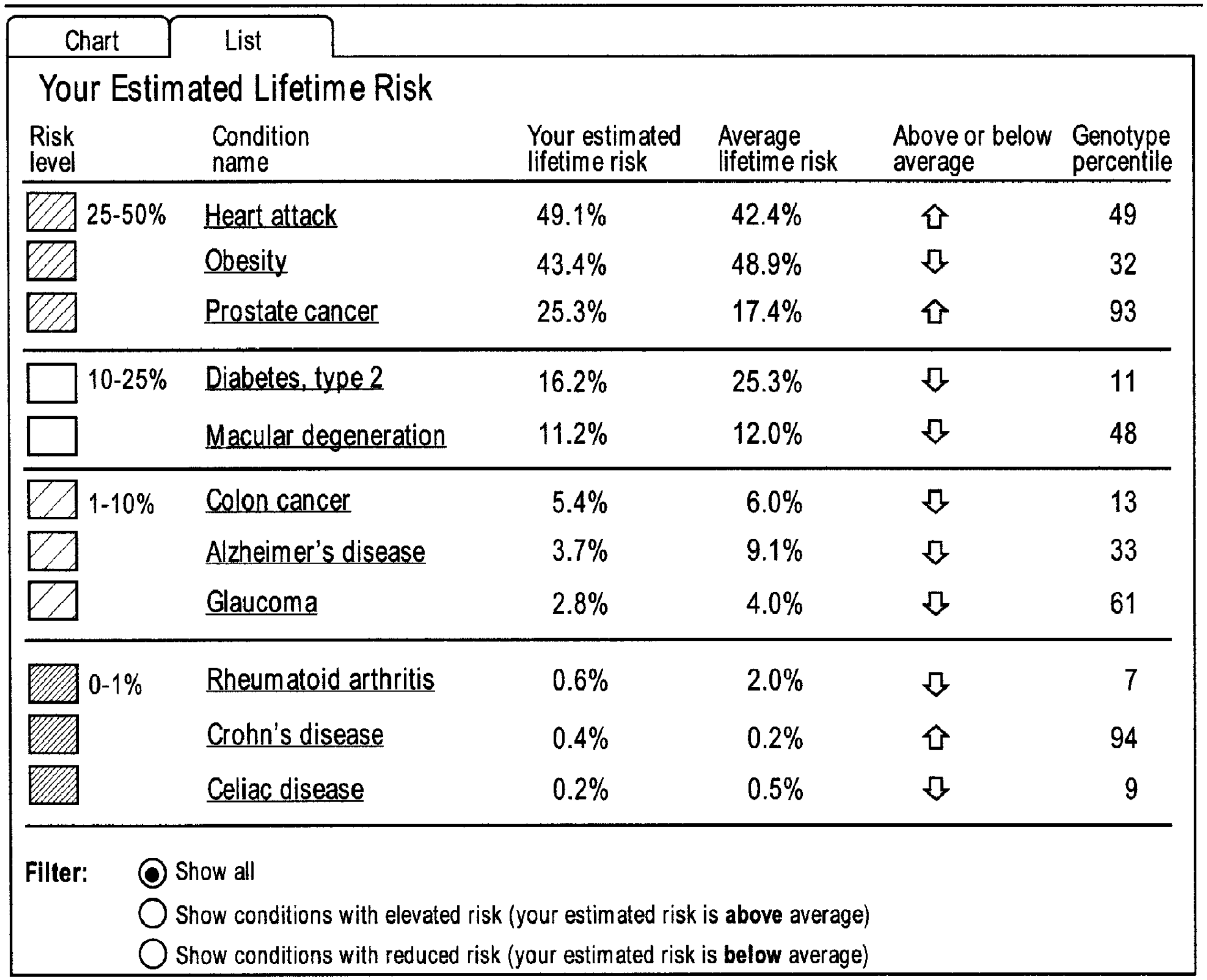


Chart
List
Your Estimated Lifetime Risk
Risk level
Condition name
Your estimated lifetime risk
Average lifetime risk
Above or below average
Genotype percentile
25-50%
Heart attack
49.1%
42.4%
49
Obesity
43.4%
48.9%
32
Prostate cancer
25.3%
17.4%
93
10-25%
Diabetes, type 2
16.2%
25.3%
11
Macular degeneration
11.2%
12.0%
48
1-10%
Colon cancer
5.4%
6.0%
13
Alzheimer's disease
3.7%
9.1%
33
Glaucoma
2.8%
4.0%
61
0-1%
Rheumatoid arthritis
0.6%
2.0%
7
Crohn's disease
0.4%
0.2%
94
Celiac disease
0.2%
0.5%
9
Filter:
Show all
Show conditions with elevated risk (your estimated risk is above average)
Show conditions with reduced risk (your estimated risk is below average)

FIG. 16A

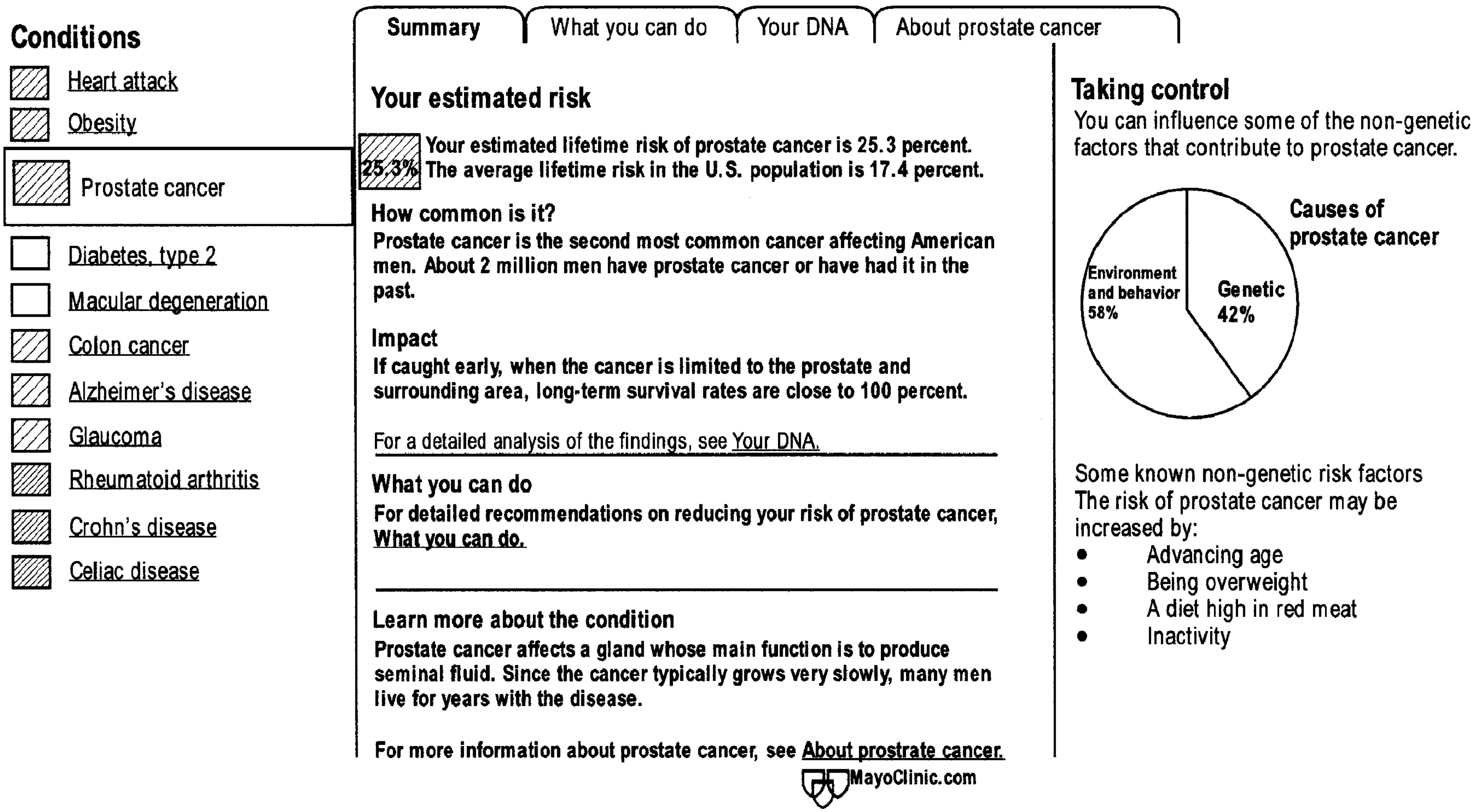

Conditions
Heart attack
Obesity
Prostate cancer
Diabetes, type 2
Macular degeneration
Colon cancer
Alzheimer's disease
Glaucoma
Rheumatoid arthritis
Crohn's disease
Celiac disease
Summary
What you can do
Your DNA
About prostate cancer
Your estimated risk
25.3%
Your estimated lifetime risk of prostate cancer is 25.3 percent.
The average lifetime risk in the U.S. population is 17.4 percent.
How common is it?
Prostate cancer is the second most common cancer affecting American men. About 2 million men have prostate cancer or have had it in the past.
Impact
If caught early, when the cancer is limited to the prostate and surrounding area, long-term survival rates are close to 100 percent.
For a detailed analysis of the findings, see Your DNA.
What you can do
For detailed recommendations on reducing your risk of prostate cancer, What you can do.
Learn more about the condition
Prostate cancer affects a gland whose main function is to produce seminal fluid. Since the cancer typically grows very slowly, many men live for years with the disease.
For more information about prostate cancer, see About prostrate cancer.
MayoClinic.com
Taking control
You can influence some of the non-genetic factors that contribute to prostate cancer.
Causes of prostate cancer
Environment and behavior 58%
Genetic 42%
Some known non-genetic risk factors
The risk of prostate cancer may be increased by:
• Advancing age
• Being overweight
• A diet high in red meat
• Inactivity

FIG. 16B

Conditions

- Heart attack
- Obesity
- Prostate cancer
- Diabetes, type 2
- Macular degeneration
- Colon cancer
- Alzheimer's disease
- Glaucoma
- Rheumatoid arthritis
- Crohn's disease
- Celiac disease

Summary | What you can do | Your DNA | About prostate cancer

Your results

Navigenics scanned your genome for 4 genetic markers that are believed to increase a person's risk of prostate cancer.

The scan show that you have 2 of the markers.
Your estimated lifetime risk of prostate cancer is 25.3 percent.
The average lifetime risk in the U.S. population is 17.4 percent.

Your results do not mean that you have prostate cancer, or that you definitely will develop it. There may be other genetic factors that have not yet been identified that you could modify your risk. Lifestyle and behavior are also important contributors to prostate cancer, and researchers believe there are steps you can take that may prevent or delay the disease.

See What you can do.

The table below shows details about your risk markers.

Published SNP	Test SNP	Accuracy	Risk Allele	Your Genotype	Odds Ratio	Citation
rs1447295	rs9643226	99.0&	C	GG	1	Yeagar. NatGen 39:645. 2007
rs16901979	rs16901979	99.5%	A	AC	1.79	Gudmundsson. NatGen 39:631. 2007
rs1859962	rs17765344	100.0%	A	AA	1.45	Gudmundsson. NatGen 39:977. 2007
rs6983267	rs6983267	100.0%	G	TT	1	Yeagar. NatGen 39:645. 2007

Notes
Roll over column headers to see explanations of the information contained in each column.

*The odds ratio was calculated for each allele.

To learn how we arrived at your estimates, see How we estimate risk.

FIG. 17A

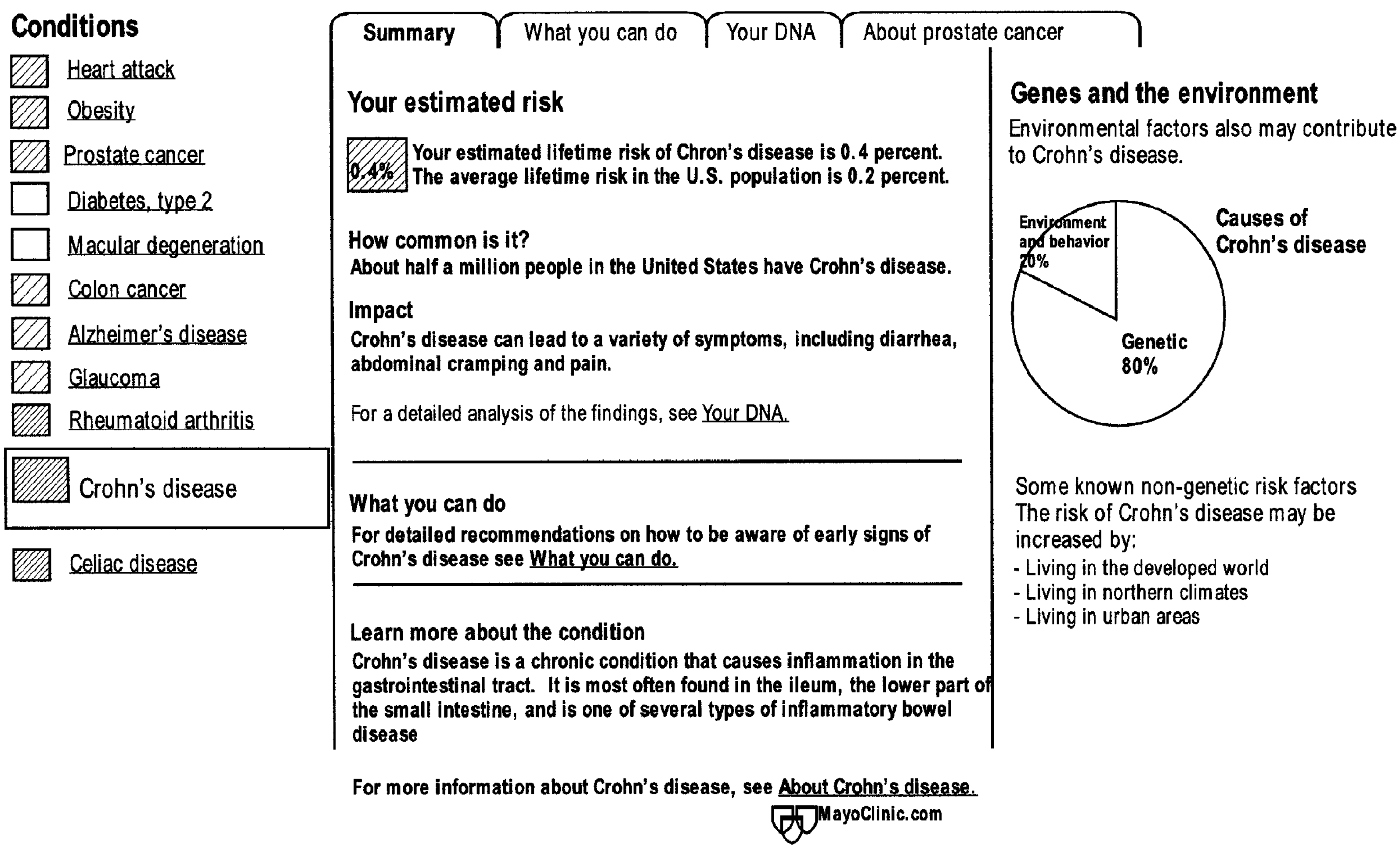

Conditions
Heart attack
Obesity
Prostate cancer
Diabetes, type 2
Macular degeneration
Colon cancer
Alzheimer's disease
Glaucoma
Rheumatoid arthritis
Crohn's disease
Celiac disease
Summary
What you can do
Your DNA
About prostate cancer
Your estimated risk
0.4%
Your estimated lifetime risk of Chron's disease is 0.4 percent.
The average lifetime risk in the U.S. population is 0.2 percent.
How common is it?
About half a million people in the United States have Crohn's disease.
Impact
Crohn's disease can lead to a variety of symptoms, including diarrhea, abdominal cramping and pain.
For a detailed analysis of the findings, see Your DNA.
What you can do
For detailed recommendations on how to be aware of early signs of Crohn's disease see What you can do.
Learn more about the condition
Crohn's disease is a chronic condition that causes inflammation in the gastrointestinal tract. It is most often found in the ileum, the lower part of the small intestine, and is one of several types of inflammatory bowel disease
For more information about Crohn's disease, see About Crohn's disease.
MayoClinic.com
Genes and the environment
Environmental factors also may contribute to Crohn's disease.
Environment and behavior 20%
Genetic 80%
Causes of Crohn's disease
Some known non-genetic risk factors
The risk of Crohn's disease may be increased by:
- Living in the developed world
- Living in northern climates
- Living in urban areas

FIG. 17B

Conditions

- Heart attack
- Obesity
- Prostate cancer
- Diabetes, type 2
- Macular degeneration
- Colon cancer
- Alzheimer's disease
- Glaucoma
- Rheumatoid arthritis
- Crohn's disease
- Celiac disease

Summary | What you can do | Your DNA | About prostate cancer

Your results

Navigenics scanned your genome for 9 genetic markers believed to increase a person's risk of Crohn's disease. The table below shows which markers we found in your DNA.

The scan show that you have 6 of the markers.
Your estimated lifetime risk of Crohn's disease is 0.4 percent.
The average lifetime risk in the U.S. population is 0.2 percent.

The table below shows details about your risk markers.

Your results do not mean that you have Crohn's disease, or that you definitely will develop it. There may be other genetic factors that have not yet been identified that you could modify your risk. However, you can be alert for early signs of the disease.

See What you can do.

Published SNP	Test SNP	Accuracy	Risk Allele	Your Genotype	Odds Ratio	Citation
rs1000113	rs1000113	100.0%	T	TT	1.92	WTCCC. Nature 447:661. 2007
rs10210302	rs10210302	100.0%	T	TT	1.85	WTCCC. Nature 447:661. 2007
rs10761659	rs10761659	100.0%	G	GG	1.55	WTCCC. Nature 447:661. 2007
rs10883365	rs10883365	100.0%	G	AG	1.2	WTCCC. Nature 447:661. 2007
rs11805303	rs11805303	100.0%	T	TC	1.39	WTCCC. Nature 447:661. 2007
rs17221417	rs17221417	100.0%	G	CC	1	WTCCC. Nature 447:661. 2007
rs17234657	rs17234657	100.0%	G	TT	1	WTCCC. Nature 447:661. 2007
rs2542151	rs2542151	100.0%	G	TT	1	WTCCC. Nature 447:661. 2007
rs9858542	rs9858542	100.0%	A	GA	1.09	WTCCC. Nature 447:661. 2007

Notes
Roll over column headers to see explanations of the information contained in each column.

FIG. 18

2 test SNPs, missing HLA locus (8 OR for RR, 2 for RN)
Lifetime risk of MS = 0.5%, 20% is +/-0.10%

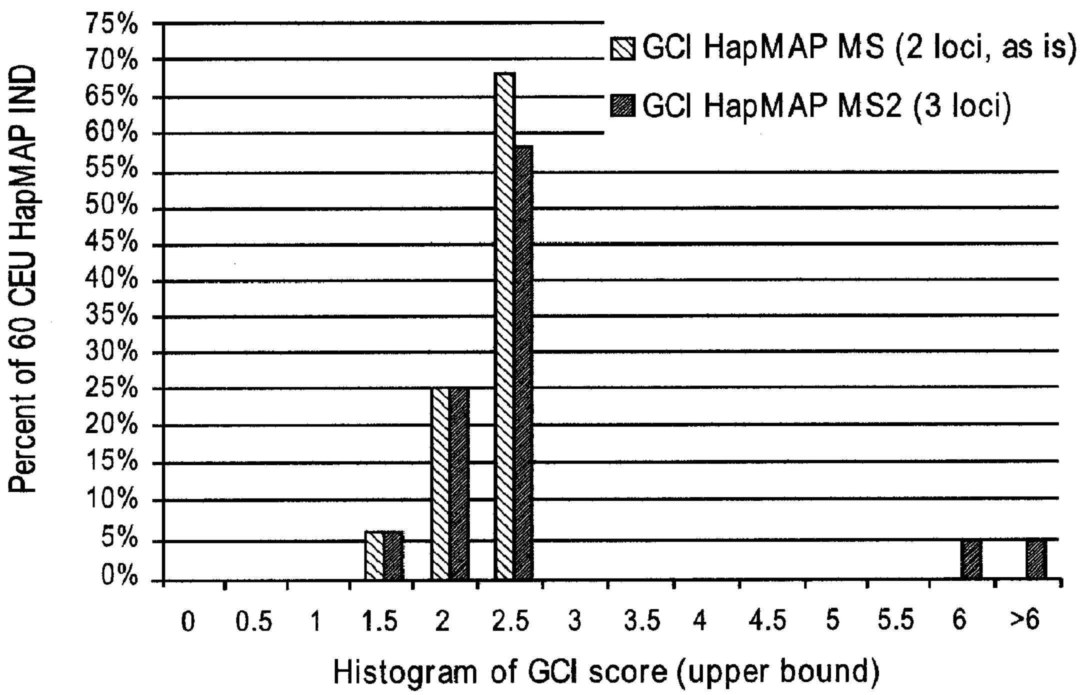


FIG. 19

Lifetime risk of MS = 0.5%

20% is +/-0.10%

IND#	LOCUS1	LOCUS2	LOCUS3	GCplus - 2 LOCi	GCplus - 3 LOCi
A	RR	RR	RR	0.6%	3.9%
B			RN	0.6%	1.5%
C			NN	0.6%	0.5%
D		RN	RR	0.5%	3.0%
E			RN	0.5%	1.1%
F			NN	0.5%	0.4%
G		NN	RR	0.4%	2.8%
H			RN	0.4%	1.1%
I			NN	0.4%	0.4%
J	RN	RR	RR	0.5%	3.1%
K			RN	0.5%	1.2%
L			NN	0.5%	0.4%
M		RN	RR	0.4%	2.4%
N			RN	0.4%	0.9%
O			NN	0.4%	0.3%
P		NN	RR	0.3%	2.3%
Q			RN	0.3%	0.9%
R			NN	0.3%	0.3%
S	NN	RR	RR	0.3%	2.2%
T			RN	0.3%	0.8%
U			NN	0.3%	0.3%
V		RN	RR	0.3%	1.7%
W			RN	0.3%	0.6%
X			NN	0.3%	0.2%
Y		NN	RR	0.2%	1.6%
Z			RN	0.2%	0.6%
AA			NN	0.2%	0.2%

Your LFT > 0.6%

Your LFT 0.4-0.6%

Your LFT < 0.4%

FIG. 20

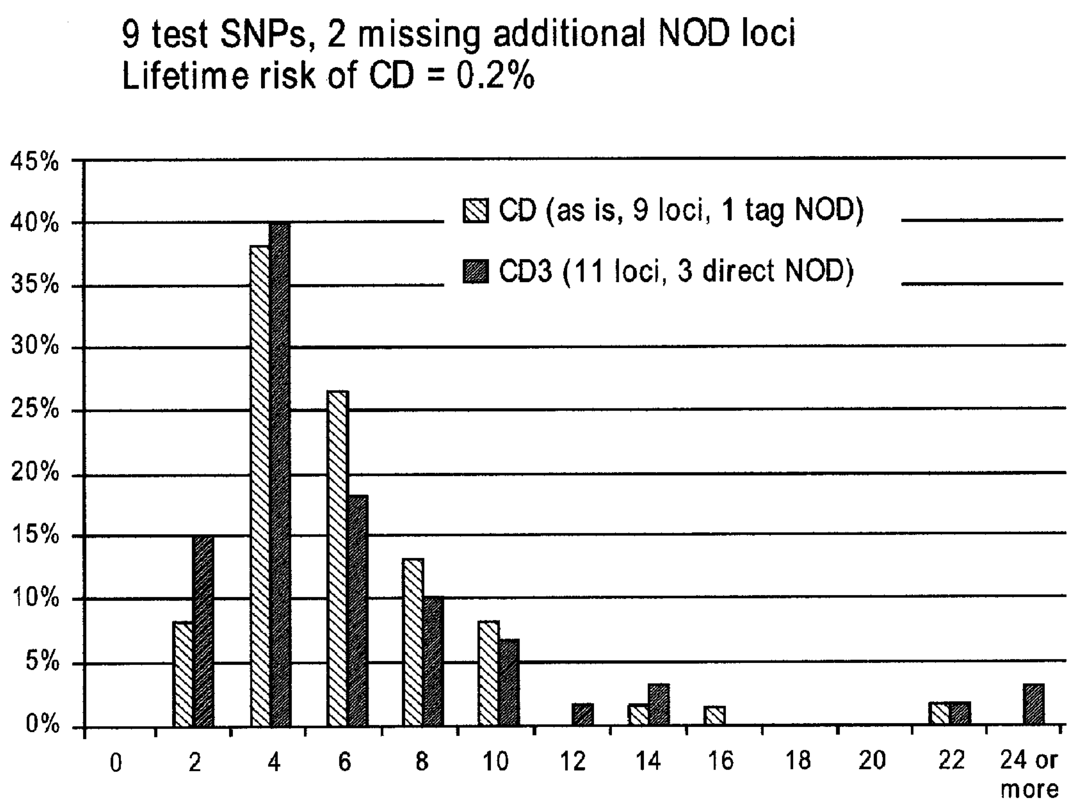

9 test SNPs, 2 missing additional NOD loci
Lifetime risk of CD = 0.2%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
CD (as is, 9 loci, 1 tag NOD)
CD3 (11 loci, 3 direct NOD)
0
2
4
6
8
10
12
14
16
18
20
22
24 or more

FIG. 21A

Multilocus Rules

Short Disease Name	Locus	Gene (or chr.loc on B36)	Gender applicability (F,M,B)	TEST SNP	Test Risk allele (plus, R)	Test NonRisk allele (plus, N)	Ethnicity/ Race-distr	UNITS for effect estimate	Effect Estimate	Effect R1R1R2 R2	Effect R1R1R2N2	Effect R1R1N2 N2
PC	PC_1 PC_2	8q24_R1 8q24_R3	M	rs4242384 rs6983267	C|G	A|T	CEU	OR (95% CI)	genotypic	3.17	2.55	2.05
HEM	HEM_1 HEM_2	HFE	B	rs1800562 rs129128	A|C	G|T	CEU	OR (95% CI)				4383

FIG. 21B

CI R1R1R2 R2	CI R1R1R2 N2	CI R1R1N2 N2	Effect R1N1R2 R2	Effect R1N1R2 N2	Effect R1N1N2 N2	CI R1N1R2 R2	CI R1N1R2 N2	CI R1N1N2 N2	Effect N1N1R2 R2	Effect N1N1R2 N2	Effect N1N1N2 N2	CI N1N1R2 R2	CI N1N1R2 N2
2.55, 3.94	2.10, 3.09	1.70, 2.46	2.22	1.78	1.43	1.91, 2.57	1.60, 1.98	1.30, 1.57	1.55	1.24	1	1.37, 1.75	1.17, 1.32
		1374, 10000		32	4.1		18.5, 55.4	2.9, 5.8	5.7	1.9	1	3.2, 10.1	1.5, 2.5

FIG. 22A

Condition	SubType	Locus	Gene (or chr.loc on B36)	Gender applicability (F,M,B)	TEST SNP	B36 Chr	B36 location	Test Risk allele (plus, R)	Test NonRisk allele (plus, N)	Ethnicity/ Race-distr
AD		AD_1	APOE	B	rs4420638	chr19	50114786	G	A	CEU
AMD		AMD_2	LOC387715	B	rs10490924	chr10	124204438	T	G	CEU
AMD		AMD_3	CFH	B	rs10737680	chr1	194946078	A	C	CEU
AMD		AMD_4	CFB-C2	B	rs541862	chr6	32024930	T	C	CEU
BC		BC_1	FGFR2	F	rs2981582	chr10	123342307	A	G	CEU
BC		BC_3	MAP3K1	F	rs4700485	chr5	56069964	A	G	CEU
BC		BC_4	LSP1	F	rs3817198	chr11	1865582	C	T	CEU
BC		BC_5	CASP8	F	rs17468277	chr2	201862445	C	T	CEU
BC	BCERP	BC_6	chr2.217614077	F	rs6721996	chr2	217617708	G	A	CEU
BC		BC_6	chr2.217614077	F	rs6721996	chr2	217617708	G	A	CEU
BC	BCERP	BC_7	TNRC9	F	rs3803662	chr16	51143842	A	G	CEU
BC		BC_7	TNRC9	F	rs3803662	chr16	51143842	A	G	CEU
BMIOB		BMIOB_1	FTO	B	rs9939609	chr16	52378028	A	T	CEU
BMIOB		BMIOB_2	GPR74	B	rs9291171	chr4	73200490	G	A	CEU
CD		CD_1	chr10.101277754	B	rs10883365	chr10	101277754	G	A	CEU
CD		CD_2	PTGER4	B	rs17234657	chr5	40437266	G	T	CEU
CD		CD_3	ATG16L1	B	rs10210302	chr2	233823578	T	C	CEU
CD		CD_4	BSN	B	rs9858542	chr3	49676987	A	G	CEU
CD		CD_5	IL23R	B	rs11805303	chr1	67448104	T	C	CEU
CD		CD_6	IRGM	B	rs1000113	chr5	150220269	T	C	CEU
CD		CD_7	NOD2 (CARD15)	B	rs17221417	chr16	49297083	G	C	CEU
CD		CD_8	PTPN2	B	rs2542151	chr18	12769947	G	T	CEU
CD		CD_9	ZNF365	B	rs10761659	chr10	64115570	G	A	CEU
CelD		CelD_1	IL2-IL22 locus	B	rs6840978	chr4	123774157	C	T	CEU

FIG. 22A (cont.)

Condition	SubType	Locus	Gene (or chr.loc on B36)	Gender applicability (F,M,B)	TEST SNP	B36 Chr	B36 location	Test Risk allele (plus, R)	Test NonRisk allele (plus, N)	Ethnicity/ Race-distr
CelD		CelD_2	HLA-DQ2.5cis	B	rs2187668	chr6	32713862	T	C	CEU
CelD		CelD_3	CTLA4	B	rs11571315	chr2	204439146	T	C	CEU
CRC		CRC_1	8q24_R3	B	rs6983267	chr8	128482487	G	T	CEU
GD		GD_1	CTLA4	B	rs3087243	chr2	204447164	G	A	CEU
HEM		HEM_1	HFE	B	rs1800562	chr6	26201120	A	G	CEU
HEM		HEM_2	HFE	B	rs129128	chr6	26233321	C	T	CEU
MI		MI_1	THBS4	B	rs1866389	chr5	79397021	G	C	CEU
MI		MI_2	9p21	B	rs1333049	chr9	22115503	C	G	CEU
MI		MI_3	MTHFD1L	B	rs6922269	chr6	151294678	A	G	CEU
MS		MS_1	IL7R	B	rs6897932	chr5	35910332	C	T	CEU
MS		MS_2	IL2R	B	rs12722489	chr10	6142018	C	T	CEU
OA	OAK	OA_1	GDF5	B	rs4911178	chr20	33416034	A	G	CHB
PC		PC_1	8q24_R1	M	rs4242384	chr8	128587736	C	A	CEU
PC		PC_2	8q24_R3	M	rs6983267	chr8	128482487	G	T	CEU
PC		PC_3	8q24_R2	M	rs16901979	chr8	128194098	A	C	CEU
PC		PC_3	8q24_R2	M	rs16901979	chr8	128194098	A	C	AfrAm
PC		PC_4	TCF2	M	rs17765344	chr17	66618469	A	G	CEU
PS		PS_1	IL12B	B	rs6859018	chr5	158669570	G	A	CEU
PS		PS_2	IL23R	B	rs11209026	chr1	67478546	G	A	CEU
RA		RA_1	PTPN22	B	rs6679677	chr1	114105331	A	C	CEU
RA	RA_RFpos	RA_1	PTPN22	B	rs6679677	chr1	114105331	A	C	CEU
RA		RA_2	MHC	B	rs6457617	chr6	32771829	T	C	CEU
RA		RA_3	PADI4	B	rs11203367	chr1	17530203	T	C	CEU
RA		RA_3	PADI4	B	rs11203367	chr1	17530203	T	C	AS

FIG. 22A (cont.)

Condition	SubType	Locus	Gene (or chr.loc on B36)	Gender applicability (F,M,B)	TEST SNP	B36 Chr	B36 location	Test Risk allele (plus, R)	Test NonRisk allele (plus, N)	Ethnicity/ Race-distr
RLS		RLS_1	MEIS1	B	rs2300478	chr2	66634957	G	T	CEU
RLS		RLS_2	MAP2k5_LBXCOR1	B	rs1026732	chr15	65882139	G	A	CEU
RLS	PLMS	RLS_3	BTBD9	B	rs6904723	chr6	38544295	A	C	CEU
RLS		RLS_3	BTBD9	B	rs9296249	chr6	38473819	T	C	CEU
SLE		SLE_1	IRF5	B	rs12531711	chr7	128404702	G	A	CEU
T2D		T2D_10	TCF7L2	B	rs4506565	chr10	114746031	T	A	CEU
T2D		T2D_11	WFS1	B	rs10012946	chr4	6344251	C	T	CEU
T2D		T2D_2	CDKAL1	B	rs7756992	chr6	20787688	G	A	CEU
T2D		T2D_2	CDKAL1	B	rs7756992	chr6	20787688	G	A	CHB
T2D		T2D_3	CDKN2A/B	B	rs10811661	chr9	22124094	T	C	CEU
T2D		T2D_4	Chr11.41871942	B	rs12288738	chr11	41868875	T	C	CEU
T2D		T2D_5	FTO	B	rs8050136	chr16	52373776	A	C	CEU
T2D		T2D_6	HHEX	B	rs1111875	chr10	94452862	C	T	CEU
T2D		T2D_7	IGF2BP2	B	rs4402960	chr3	186994381	T	G	CEU
T2D		T2D_8	KCNJ11	B	rs5215	chr11	17365206	C	T	CEU
T2D		T2D_9	PPARG	B	rs1801282	chr3	12368125	C	G	CEU
XFG		XFG_1	LOXL1	B	rs2165241	chr15	72009255	T	C	CEU

FIG. 22B

Condition	Published SNP	Published Risk allele (plus)	Published Non Risk allele (plus)	Units for Effect Estimate	Effect Estimate	Genotypic risk: risk homoz (RR vs NN)	RR confidence interval	Genotypic risk: risk heteroz (RN vs NN)	RN confidence interval	Genotypic risk: nonrisk homoz (NN vs NN)	Carrier Risk (RR or RN vs NN)
AD	rs4420638	G	A	OR (95% CI)	genotypic	17.99	8.95, 36.19	4.00	3.00, 5.34	1.00	
AMD	rs10490924	T	G	OR (95% CI)	genotypic	10.57		2.72		1.00	
AMD	rs1410996	G	A	OR (95% CI)	allelic						
AMD	rs641153	G	A	OR (95% CI)	genotypic	6.98	0.72, 67.50	2.33	0.23, 23.25	1.00	
BC	rs2981582	A	G	OR (95% CI)	genotypic	1.63	1.53, 1.72	1.23	1.18, 1.28	1.00	
BC	rs889312	C	A	OR (95% CI)	genotypic	1.27	1.19, 1.36	1.13	1.09, 1.18	1.00	
BC	rs3817198	C	T	OR (95% CI)	genotypic	1.17	1.08, 1.25	1.06	1.02, 1.11	1.00	
BC	rs1045485	G	C	OR (95% CI)	genotypic	1.35	1.15, 1.61	1.12	1.06, 1.18	1.00	
BC	rs13387042	A	G	OR (95% CI)	allelic						
BC	rs13387042	A	G	OR (95% CI)	genotypic	1.44	1.30, 1.58	1.11	1.03, 1.20	1.00	
BC	rs3803662	A	G	OR (95% CI)	allelic						
BC	rs3803662	A	G	OR (95% CI)	genotypic	1.64	1.45, 1.85	1.27	1.19, 1.36	1.00	
BMIOB	rs9939609	A	T	OR (95% CI)	genotypic	1.74	1.60, 1.89	1.31	1.23, 1.39	1.00	
BMIOB	rs9291171	G	A	OR (95% CI)	genotypic	1.53	1.12, 2.10	1.24	1.04, 1.47	1.00	
CD	rs10883365	G	A	OR (95% CI)	genotypic	1.62	1.37, 1.92	1.20	1.03, 1.39	1.00	
CD	rs17234657	G	T	OR (95% CI)	genotypic	2.32	1.59, 3.39	1.54	1.34, 1.76	1.00	
CD	rs10210302	T	C	OR (95% CI)	genotypic	1.85	1.56, 2.21	1.19	1.01, 1.41	1.00	
CD	rs9858542	A	G	OR (95% CI)	genotypic	1.84	1.49, 2.26	1.09	0.96, 1.24	1.00	
CD	rs11805303	T	C	OR (95% CI)	genotypic	1.86	1.54, 2.24	1.39	1.22, 1.58	1.00	
CD	rs1000113	T	C	OR (95% CI)	genotypic	1.92	0.92, 4.00	1.54	1.31, 1.82	1.00	
CD	rs17221417	G	C	OR (95% CI)	genotypic	1.92	1.58, 2.34	1.29	1.13, 1.46	1.00	
CD	rs2542151	G	T	OR (95% CI)	genotypic	2.01	1.46, 2.76	1.30	1.13, 1.48	1.00	
CD	rs10761659	G	A	OR (95% CI)	genotypic	1.55	1.30, 1.84	1.23	1.05, 1.45	1.00	
CelD	rs6840978	C	T	OR (95% CI)	allelic						

FIG. 22B (cont.)

Condition	Published SNP	Published Risk allele (plus)	Published Non Risk allele (plus)	Units for Effect Estimate	Effect Estimate	Genotypic risk: risk homoz (RR vs NN)	RR confidence interval	Genotypic risk: risk heteroz (RN vs NN)	RN confidence interval	Genotypic risk: nonrisk homoz (NN vs NN)	Carrier Risk (RR or RN vs NN)
CelD	rs2187668	T	C	OR (95% CI)	allelic						
CelD	rs231779	T	C	OR (95% CI)	allelic						
CRC	rs6983267	G	T	OR (95% CI)	genotypic	1.47	1.25, 1.74	1.04	0.90, 1.20	1	
GD	rs3087243	G	A	OR (95% CI)	genotypic	2.32	1.71, 3.15	1.59	1.19, 2.13	1	
HEM	rs1800562	A	G		multilocus						
HEM	rs1799945	G	C		multilocus						
MI	rs1866389	G	C	OR (95% CI)	genotypic	3.07	1.32, 7.13	1.16	0.78, 1.73	1.00	
MI	rs10757278	G	A	OR (95% CI)	genotypic	1.72	1.45, 2.03	1.28	1.14, 1.45	1.00	
MI	rs6922269	A	G	OR (95% CI)	genotypic	1.53	1.28, 1.83	1.23	1.11, 1.36	1	
MS	rs6897932	C	T	OR (95% CI)	genotypic	1.8	1.37, 2.35	1.46	1.11, 1.92	1	
MS	rs12722489	C	T	OR (95% CI)	genotypic	1.37	1.03, 1.80	1.06	0.80, 1.41	1	
OA	rs143383	A	G	OR (95% CI)	genotypic	2.04	1.16, 3.58	1.27	0.71, 2.28	1.00	
PC	rs1447295	A	C	OR (95% CI)	genotypic	2.23	1.58, 3.14	1.43	1.29, 1.59	1.00	
PC	rs6983267	G	T	OR (95% CI)	genotypic	1.58	1.40, 1.78	1.26	1.13, 1.41	1.00	
PC	rs16901979	A	C	OR (95% CI)	allelic						
PC	rs16901979	A	C	OR (95% CI)	allelic						
PC	rs1859962	G	T	OR (95% CI)	genotypic	1.45	1.29, 1.62	1.33	1.21, 1.44	1.00	
PS	rs3212227	T	G	OR (95% CI)	genotypic	2.55	1.52, 4.28	1.47	0.86, 2.5	1	
PS	rs11209026	G	A	OR (95% CI)	allelic						
RA	rs2476601	A	G	OR (95% CI)	genotypic	2.26	0.56, 9.14	1.69	1.23, 2.32	1.00	
RA	rs2476601	A	G	OR (95% CI)	carrier						1.71
RA	rs6457617	T	C	OR (95% CI)	genotypic	5.21	4.31, 6.30	2.36	1.97, 2.84	1.00	
RA	rs2240340	T	C	OR (95% CI)	genotypic	2.1	1.66, 2.66	1.12	0.91, 1.98	1	
RA	rs2240340	T	C	OR (95% CI)	genotypic	3.19	2.52, 4.03	1.32	1.14, 1.53	1	

FIG. 22B (cont.)

Condition	Published SNP	Published Risk allele (plus)	Published Non Risk allele (plus)	Units for Effect Estimate	Effect Estimate	Genotypic risk: risk homoz (RR vs NN)	RR confidence interval	Genotypic risk: risk heteroz (RN vs NN)	RN confidence interval	Genotypic risk: nonrisk homoz (NN vs NN)	Carrier Risk (RR or RN vs NN)
RLS	rs2300478	G	T	OR (95% CI)	genotypic	3.32	2.64, 4.18	1.82	1.59, 2.09	1	
RLS	rs1026732	G	A	OR (95% CI)	genotypic	2.08	1.62, 2.66	1.44	1.12, 1.86	1	
RLS	rs6904723	A	C	OR (95% CI)	genotypic	2.58	1.78, 3.74	1.86	1.30, 2.67	1	
RLS	rs9296249	T	C	OR (95% CI)	genotypic	2.85	1.93, 4.20	1.67	1.45, 1.92	1	
SLE	rs2070197	C	T	OR (95% CI)	allelic						
T2D	rs4506565	T	A	OR (95% CI)	genotypic	1.88	1.56, 2.27	1.36	1.20, 1.54	1.00	
T2D	rs10010131	G	A	OR (95% CI)	genotypic	1.19	1.10, 1.30	1.03	0.95, 1.12	1	
T2D	rs7756992	G	A	OR (95% CI)	genotypic	1.5	1.31, 1.72	1.15	1.06, 1.24	1.00	
T2D	rs7756992	G	A	OR (95% CI)	genotypic	1.52	1.21, 1.90	1.27	1.05, 1.55	1.00	
T2D	rs10811661	T	C	OR (95% CI)	genotypic	1.39	1.13, 1.71	1.16	0.94, 1.43	1.00	
T2D	rs9300039	C	A	OR (95% CI)	genotypic	2.61	1.33, 5.11	1.80	0.91, 3.57	1.00	
T2D	rs8050136	A	C	OR (95% CI)	genotypic	1.49	1.33, 1.68	1.15	1.06, 1.26	1.00	
T2D	rs1111875	C	T	OR (95% CI)	genotypic	1.2	1.10, 1.31	1.06	0.98, 1.16	1.00	
T2D	rs4402960	T	G	OR (95% CI)	genotypic	1.21	1.10, 1.34	1.16	1.09, 1.24	1.00	
T2D	rs5219	T	C	OR (95% CI)	genotypic	1.22	1.04, 1.44	1.12	0.98, 1.28	1.00	
T2D	rs1801282	C	G	OR (95% CI)	genotypic	1.53	1.08, 2.16	1.30	0.91, 1.86	1.00	
XFG	rs2165241	T	C	OR (95% CI)	genotypic	16.54	9.40, 29.11	3.72	2.07, 6.68	1	

FIG. 22C

Condition	RR or RN confidence interval	Allelic Risk (R vs N)	R confidence interval	Seminal publication	DIRECT or TAG SNP	Published SNP B36 Chr	Published SNP B36 Location	Published Minor allele (plus)	Published Major allele (plus)	Test SNP accuracy Rate
AD				Coon. J Clin Psychiatry 68:4. 2007	TAG	chr19	50114786	G	A	100.0%
AMD				Jakobsdottir. AJHG 77:389. 2005	DIRECT	chr10	124204438	T	G	99.5%
AMD		3.16		Maller. NatGen 38:1055. 2007	TAG	chr1	194963556	A	G	100.0%
AMD				Gold. Nat Genet 38:45. 2006.	TAG	chr6	32022159	A	G	100.0%
BC				Easton. Nature 447:1087. 2007	DIRECT	chr10	123342307	A	G	100.0%
BC				Easton. Nature 447:1087. 2007	TAG	chr5	56067641	C	A	100.0%
BC				Easton. Nature 447:1087. 2007	DIRECT	chr11	1865582	C	T	100.0%
BC				Cox. NatGen 39:352. 2007.	TAG	chr2	201857834	C	G	100.0%
BC		1.22	1.14, 1.31	Stacey. NatGen 39:865. 2007	TAG	chr2	217614077	G	A	100.0%
BC		1.2	1.14, 1.26	Stacey. NatGen 39:865. 2007	TAG	chr2	217614077	G	A	100.0%
BC		1.32	1.22, 1.42	Stacey. NatGen 39:865. 2007	DIRECT	chr16	51143842	A	G	100.0%
BC		1.28	1.21, 1.35	Stacey. NatGen 39:865. 2007	DIRECT	chr16	51143842	A	G	100.0%
BMIOB				Frayling. Science 316:889. 2007	DIRECT	chr16	52378028	A	T	100.0%
BMIOB				Dahlman. AJHG 80:1115. 2007.	DIRECT	chr4	73200490	G	A	100.0%
CD				WTCCC. Nature 447:661. 2007	DIRECT	chr10	101277754	G	A	100.0%
CD				WTCCC. Nature 447:661. 2007	DIRECT	chr5	40437266	G	T	100.0%
CD				WTCCC. Nature 447:661. 2007	DIRECT	chr2	233823578	C	T	100.0%
CD				WTCCC. Nature 447:661. 2007	DIRECT	chr3	49676987	A	G	100.0%
CD				WTCCC. Nature 447:661. 2007	DIRECT	chr1	67448104	T	C	100.0%
CD				WTCCC. Nature 447:661. 2007	DIRECT	chr5	150220269	T	C	100.0%
CD				WTCCC. Nature 447:661. 2007	TAG	chr16	49297083	G	C	100.0%
CD				WTCCC. Nature 447:661. 2007	DIRECT	chr18	12769947	G	T	100.0%
CD				WTCCC. Nature 447:661. 2007	DIRECT	chr10	64115570	A	G	100.0%
CelD		1.42	1.28, 1.59	van Heel. Nat Genet 39:827. 2007	DIRECT	chr4	123774157	T	C	100.0%

FIG. 22C (cont.)

Condition	RR or RN confidence interval	Allelic Risk (R vs N)	R confidence interval	Seminal publication	DIRECT or TAG SNP	Published SNP B36 Chr	Published SNP B36 Location	Published Minor allele (plus)	Published Major allele (plus)	Test SNP accuracy Rate
CelD		7.04	6.08, 8.15	van Heel. Nat Genet 39:827. 2007	DIRECT	chr6	32713862	T	C	100.0%
CelD		1.24	1.04, 1.49	Hunt. EJHG 13:440. 2005; van Heel. Nat Genet 39:827. 2007	TAG	chr2	204442732	T	C	100.0%
CRC				Haiman. NatGen July 8, 2007	DIRECT	chr8	128482487	G	T	100.0%
GD				Ueda. Nature 423:506. 2003	DIRECT	chr2	204447164	A	G	100.0%
HEM				Burke. Gen Med 2:271. 2000	DIRECT	chr6	26201120	A	G	100.0%
HEM				Burke. Gen Med 2:271. 2000	TAG	chr6	26199158	G	C	100.0%
MI				Wessel. AHJ 147:905. 2004	DIRECT	chr5	79397021	C	G	100.0%
MI				Helgadottir. Science 316:1491. 2007.	TAG	chr9	22114477	G	A	100.0%
MI				Samani. NEJM July 2007	DIRECT	chr6	151294678	A	G	100.0%
MS				Gregory. NatGen AOP 7/29/07	DIRECT	chr5	35910332	T	C	100.0%
MS				Intl MS Cons. NEJM 7/29/07	DIRECT	chr10	6142018	T	C	100.0%
OA				Miyamoto. NatGen 39:539 2007	TAG	chr20	33489397	G	A	100.0%
PC				Yeagar. NatGen 39:645. 2007	TAG	chr8	128554220	A	C	100.0%
PC				Yeagar. NatGen 39:645. 2007	DIRECT	chr8	128482487	G	T	100.0%
PC		1.79	1.53, 2.11	Gudmundsson. NatGen 39:631. 2007	DIRECT	chr8	128194098	A	C	99.5%
PC		1.34	1.09, 1.64	Gudmundsson. NatGen 39:631. 2007	DIRECT	chr8	128194098	A	C	99.5%
PC				Gudmundsson. NatGen 39:977. 2007	TAG	chr17	66620348	G	T	100.0%
PS				Cargill. AJHG 80:273. 2007	TAG	chr5	158675528	G	T	98.9%
PS		1.59	1.27, 2.00	Cargill. AJHG 80:273. 2007	DIRECT	chr1	67478546	A	G	100.0%
RA				Begovich. AJHG. 75:330. 2004	TAG	chr1	114179091	A	G	100.0%
RA	1.25, 2.34			Begovich. AJHG. 75:330. 2004	TAG	chr1	114179091	A	G	100.0%
RA				WTCCC. Nature 447:661. 2007	DIRECT	chr6	32771829	T	C	100.0%
RA				Lee. RheumInt 27:827. 2007	TAG	chr1	17535226	T	C	100.0%

FIG. 22C (cont.)

Condition	RR or RN confidence interval	Allelic Risk (R vs N)	R confidence interval	Seminal publication	DIRECT or TAG SNP	Published SNP B36 Chr	Published SNP B36 Location	Published Minor allele (plus)	Published Major allele (plus)	Test SNP accuracy Rate
RA				Lee. RheumInt 27:827. 2007	TAG	chr1	17535226	T	C	100.0%
RLS				Winkelman. Nat Genet July 2007.	DIRECT	chr2	66634957	G	T	100.0%
RLS				Winkelman. Nat Genet July 2007.	DIRECT	chr15	65882139	A	G	100.0%
RLS				Stefansson. NEJM 357. July 18, 2007	DIRECT	chr6	38544295	C	A	100.0%
RLS				Winkelman. Nat Genet July 2007.	DIRECT	chr6	38473819	C	T	100.0%
SLE		2.04	1.52, 2.74	Graham. PNAS 104:6758. 2007	TAG	chr7	128376236	C	T	100.0%
T2D				WTCCC. Nature 447:661. 2007	DIRECT	chr10	114746031	T	A	100.0%
T2D				Sandhu. NatGen July 1 2007.	TAG	chr4	6343816	A	G	100.0%
T2D				Steinthorsdottir. Nat Genet 39:770. 2007.	DIRECT	chr6	20787688	G	A	100.0%
T2D				Steinthorsdottir. Nat Genet 39:770. 2007.	DIRECT	chr6	20787688	G	A	100.0%
T2D				Scott. Science 316.1341. 2007; Zeggini. Science 316:1336. 2007	DIRECT	chr9	22124094	C	T	100.0%
T2D				Scott. Science 316.1341. 2007.	TAG	chr11	41871942	A	C	100.0%
T2D				Zeggini. Science 316:1336. 2007	DIRECT	chr16	52373776	A	C	100.0%
T2D				Scott. Science 316.1341. 2007.	DIRECT	chr10	94452862	T	C	100.0%
T2D				Scott. Science 316.1341. 2007.	DIRECT	chr3	186994381	T	G	100.0%
T2D				Scott. Science 316.1341. 2007.	TAG	chr11	17366148	T	C	100.0%
T2D				Scott. Science 316.1341. 2007.	DIRECT	chr3	12368125	G	C	100.0%
XFG				Thorleifsson. Science Express Aug 9, 2007	DIRECT	chr15	72009255	T	C	100.0%

FIG. 23A

Name	Condition or SubType	Disease	Product Disease Name	Gender applicability of the condition	Product	Overall Heritability	Male Heritability	Female Heritability	Heritability Condition	Heritability Reference
AD	Condition	Alzheimer's Disease	Alzheimer's Disease	B	FandF	0.62			Alzheimer's Disease	The Genetic Basis of Common Diseases, 2ed. Ed: R. King, J. Rot-ter, A. Motulsky, 2002
AMD	Condition	Age Related Macular Degeneration	macular degeneration	B	FandF	0.67			Macular degeneration (stage 3-5)	Haddad. Sur-vey of Opthalmology 51:316. 2006
BC	Condition	Breast Cancer	breast cancer	F	FandF			0.27	Breast Cancer	Lichtenstein. NEJM 343:78. 2000
BCERP	SubType	breast cancer, estrogen receptor positive								

FIG. 23A (cont.)

Name	Condition or SubType	Disease	Product Disease Name	Gender applicability of the condition	Product	Overall Heritability	Male Heritability	Female Heritability	Heritability Condition	Heritability Reference
BMIOB	Condition	Body Mass Index, obesity endpoint (BMI≥30kg/m^2)	obesity	B	FandF	0.67			BMI	The Genetic Basis of Common Diseases, 2ed. Ed: R. King, J. Rotter, A. Motulsky, 2002
CD	Condition	Crohn's disease	Crohn's disease	B	FandF	0.80			Crohn's disease	Tysk. Gut 29:990. 1988
CelD	Condition	Celiac disease	celiac disease	B	FandF	0.57			Celiac disease	Nistico. Gut 55:803. 2006
CRC	Condition	Colorectal cancer	colon cancer	B	FandF	0.35			Colon cancer	Lichtenstein. NEJM 343:78. 2000
GD	Condition	Graves' disease	Graves' disease	B		0.64			Graves' disease	Brix. J Clin Endocrinol Metab 86:930. 2001

FIG. 23A (cont.)

Name	Condition or SubType	Disease	Product Disease Name	Gender applicability of the condition	Product	Overall Heritability	Male Heritability	Female Heritability	Heritability Condition	Heritability Reference
HEM	Condition	hemochromatosis	hemochromatosis	B						The Genetic Basis of Common Diseases, 2ed. Ed: R. King, J. Rotter, A. Motulsky, 2002
MI	Condition	Myocardial infarction	heart attack	B	FandF		0.57	0.38	Death from MI	Zdravkovic. J Int Med 252:247. 2002.
MS	Condition	Multiple Sclerosis	multiple sclerosis	B		0.48			multiple sclerosis	Ebers. NEJM 315:150. 1986
OA	Condition	osteoarthritis	osteoarthritis	B				0.54	osteoarthritis	Spector. BMJ 312:940. 1996
PC	Condition	Prostate Cancer	prostate cancer	M	FandF		0.42		prostate cancer	Lichtenstein. NEJM 343:78. 2000

FIG. 23A (cont.)

Name	Condition or SubType	Disease	Product Disease Name	Gender applicability of the condition	Product	Overall Heritability	Male Heritability	Female Heritability	Heritability Condition	Heritability Reference
PLMS	SubType	Periodic Limb Movements in Sleep with restless leg syndrome (majority subset)								
PS	Condition	Psoriasis	psoriasis	B		0.65			psoriasis	Watson. Arch Dermatol 105:197. 1972.
RA	Condition	rheumatoid arthritis	rheumatoid arthritis	B	FandF	0.53			rheumatoid arthritis	MacGregor. Arthritis Rheumatism 43:30. 2000
RA_RF pos	SubType	Rheumatoid arthritis, RF factor positive								
RLS	Condition	Restless Leg Syndrome	restless leg syndrome	B		0.60			restless leg syndrome	Chen. AJHG 74:876. 2004.

FIG. 23A (cont.)

Name	Condition or SubType	Disease	Product Disease Name	Gender applicability of the condition	Product	Overall Heritability	Male Heritability	Female Heritability	Heritability Condition	Heritability Reference
SLE	Condition	Systemic lupus erythamatosus	lupus	B		0.62			lupus	The Genetic Basis of Common Diseases, 2ed. Ed: R. King, J. Rotter, A. Motulsky, 2002
T2D	Condition	Diabetes, Type 2	diabetes, type 2	B	FandF	0.64			Diabetes, type 2	The Genetic Basis of Common Diseases, 2ed. Ed: R. King, J. Rotter, A. Motulsky, 2002
XFC	Condition	exfoliation glaucoma	glaucoma	B	FandF	0.13			Open angle glaucoma	Teikari. Acta Opthalmol 65:175. 1987.

FIG. 23B

Name	Overall Prev	Male Prevalence	Female Prevalence	Prevalence to use in GCI AND GCI+ and copy	Prevalence Reference	Overall LTR	Male LTR	Female LTR	LTR Reference	Age category for LTR	LTR curator
AD	0.015	0.0117	0.0300	overall	Neurology 42:115 1992		0.091	0.172	Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, Wolf PA. The lifetime risk of stroke: estimates from the Framingham Study. Stroke. 2006 Feb;37(2):345-50. Epub 2006 Jan 5	65-74	JW
AMD	0.0147	0.0103	0.0180	overall	Archives of Opth. 122:564. 2004.	0.12			Klaver CC, Wolfs RC, Assink JJ, van Duijn CM, Hofman A, de Jong PT. Genetic risk of age-related maculopathy. Population-based familial aggregation study. Arch Ophthalmol. 1998 Dec;116(12):1646-51.		DS
BC	0.0083	0.0001	0.0082	female	SEER Cancer Statistics Review 1975-2003, National Cancer Institute			0.1315	SEER Cancer Statistics Review 1975-2003, National Cancer Institute, http://seer.cancer.gov/csr/1975_2003/results_merged/topic_lifetime_risk.pdf	40-49	JW
BCERP											
BMIOB	0.2390	0.2420	0.2350	overall	MMWR September 15, 2006 / 55(36); 985-988		0.489	0.456	Vasan RS, Pencina MJ, Cobain M, Freiberg MS, D'Agostino RB. Estimated risks for developing obesity in the Framingham Heart Study. Ann Intern Med. 2005 Oct 4;143(7):473-80.	40-49	JW
CD	0.0015			overall	www.cdc.gov/foodborne/publications/24_ashford_2001.pdf	0.002					DS
CelD	0.0067			overall	http://digestive.niddk.nih.gov/ddiseases/pubs/celiac/#7	0.005					DS

FIG. 23B (cont.)

Name	Overall Prev	Male Prevalence	Female Prevalence	Prevalence to use in GCI AND GCI+ and copy	Prevalence Reference	Overall LTR	Male LTR	Female LTR	LTR Reference	Age category for LTR	LTR curator
CRC	0.0037	0.0036	0.0038	overall	SEER Cancer Statistics Review 1975-2003, National Cancer Institute		0.0599	0.0541	SEER Cancer Statistics Review 1975-2003, National Cancer Institute, http://seer.cancer.gov/csr/1975_2003/results_merged/topic_lifetime_risk.pdf	40-49	JW
GD	0.0147	0.0023	0.0270	overall	Inherited Basis of Common Disease						
HEM	0.0033			overall	http://ghr.nlm.nih.gov/condition=hemochromatosis						
MI	0.0400	0.0550	0.0290	overall	MMWR February 16, 2007 / 56(06);113-118		0.424	0.249	Lloyd-JonesDM, Lancet 1999	40-49	JW
MS	0.0010			overall	"No one knows exactly how many people have MS. It is believed that, currently, there are approximately 250,000 to 350,000 people in the United States with MS diagnosed by a physician." www.ninds.nih.goc/disorders/multiple_sclerosis/detail_multiple_sclerosis.htm#80483215						
OA	0.0950	0.0680	0.1140	overall	Arth and Rheum 41:778 1998	0.24					DS
PC		0.0133		male	SEER Cancer Statistics Review 1975-2003, National Cancer Institute		0.1735		SEER Cancer Statistics Review 1975-2003, National Cancer Institute, http://seer.cancer.gov/csr/1975_2003/results_merged/topic_lifetime_risk.pdf	40-49	JW
PLMS						0.08					DS

FIG. 23B (cont.)

Name	Overall Prev	Male Prevalence	Female Prevalence	Prevalence to use in GCI AND GCI+ and copy	Prevalence Reference	Overall LTR	Male LTR	Female LTR	LTR Reference	Age category for LTR	LTR curator
PS	0.0220			overall	"Psoriasis is a chronic (long-lasting) skin disease of scaling and inflam-mation that affects 2 to 2.6 percelt of the United States population, or between 5.8 and 7.5 million people." www.niams.nih. gov/hi/topics/ psoriasis/psoriasis.htm	0.04					DS
RA	0.0110	0.0070	0.0140	overall	Arth and Rheum 42:415 1999	0.02					DS
RA_RFpos											
RLS	0.1060	0.0990	0.0112	overall	Sleep Med. 7:545 2006	0.1					DS
SLE	0.0010	0.0001	0.0020	overall	Arth and Rheum 41:778 1998	0.0014					DS
T2D	0.0740	0.0780	0.0710	overall	CDC. 2005 NH survey.		0.253	0.277	Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF. Lifetime risk for diabetes mellitus in the United States.JAMA. 2003 Oct 8; 290(14):1884-90.	40-49	JW
XFG	0.0190			overall	http://www.nei.nih.gov/eyedata/pbd_tables.asp	0.04					DS

FIG. 24

Glossary

Abbreviation	What Does it stand for?
CEU	European/Caucasian ethnicity
CHB	Chinese ethnicity
JAP	Japanese ethnicity
YRI	Yoruban ethnicity
R	risk allele
N	non-risk allele
CC	case control study design
Ethnicity	
C(H)	Han Chinese ethnicity
E	European
J	Japanese
L	Latino
NA-P	Native American-Pima Indians
H	Hawaiian
Af	African
As	Asian
AfrAm	African Americans
JapAm	Japanese Americans
EurAm	European Americans
Ash	Ashkenazi
Countries	
CH	Switzerland
Dk	Denmark
FI	Finland
GH	Ghana
IS	Iceland
IT	Italy
KR	Korea
NG	Nigeria
NL	Netherlands
GB	United Kingdom
FR	France
ES	Spain
SE	Sweden
TH	Thailand
TW	Taiwan
US	United States
DE	Germany
CA	Canada
BE	Belgium

FIG. 25A

Condition	Sub Type	Locus	Gene (or chr.loc on B36)	TEST SNP	B36 Chr	B36 location	Test Risk allele (plus, R)	Test Non Risk allele (plus, N)	Ethnicity/ Race-distr
AD		AD_1	APOE	rs4420638	chr19	50114786	G	A	CEU
AMD		AMD_1	C3-R80G						CEU
AMD		AMD_5	CFH-Y402H						CEU
AMD		AMD_6	C2-E318D						CEU
AMD		AMD_3	CFH	rs10737680	chr1	194946078	A	C	CEU
AMD		AMD_2	LOC387715-S69A	rs10490924	chr10	124204438	T	G	CEU
AMD		AMD_4	CFB	rs541862	chr6	32024930	T	C	CEU
BC	BCERP	BC_6	chr2.217614077	rs6721996	chr2	217617708	G	A	CEU
BC	BCERP	BC_7	TNRC9	rs3803662	chr16	51143842	A	G	CEU
BC		BC_1	FGFR2	rs2981582	chr10	123342307	A	G	CEU
BC		BC_3	MAP3KL	rs4700485	chr5	56069964	A	G	CEU
BC		BC_4	LSPL	rs3817198	chr11	1865582	C	T	CEU
BC		BC_5	CASP8	rs17468277	chr2	201862445	C	T	CEU
BC		BC_6	chr2.217614077	rs6721996	chr2	217617708	G	A	CEU
BC		BC_7	TNRC9	rs3803662	chr16	51143842	A	G	CEU
BMIOB		BMIOB_1	FTO	rs9939609	chr16	52378028	A	T	CEU
BMIOB		BMIOB_2	GPR74	rs9291171	chr4	73200490	G	A	CEU
CD		CD_10	NOD2 (CARD15)						CEU
CD		CD_11	NOD2 (CARD15)						CEU
CD		CD_1	chr10.101277754	rs10883365	chr10	101277754	G	A	CEU
CD		CD_2	PTGER4	rs17234657	chr5	40437266	G	T	CEU
CD		CD_3	ATG16L1	rs10210302	chr2	233823578	T	C	CEU
CD		CD_4	BSN	rs9858542	chr3	49676987	A	G	CEU
CD		CD_5	IL23R	rs11805303	chr1	67448104	T	C	CEU
CD		CD_6	IRGM	rs1000113	chr5	150220269	T	C	CEU
CD		CD_7	NOD2 (CARD15)	rs17221417	chr16	49297083	G	C	CEU

FIG. 25A (cont.)

Condition	Sub Type	Locus	Gene (or chr.loc on B36)	TEST SNP	B36 Chr	B36 location	Test Risk allele (plus, R)	Test Non Risk allele (plus, N)	Ethnicity/ Race-distr
CD		CD_8	PTPN2	rs2542151	chr18	12769947	G	T	CEU
CD		CD_9	ZNF365	rs10761659	chr10	64115570	G	A	CEU
CelD		CelD_4	HLA-DQ8:1						CEU
CelD		CelD_1	IL2-IL22 locus	rs6840978	chr4	123774157	C	T	CEU
CelD		CelD_3	CTLA4	rs11571315	chr2	204439146	T	C	CEU
CelD		CelD_2	HLA-DQ2.5	rs2187668	chr6	32713862	T	C	CEU
CRC		CRC_1	8q24_R3	rs6983267	chr8	128482487	G	T	CEU
GD		GD_2	DRB1*0301 DQAI*0501						CEU
GD		GD_1	CTLA4	rs3087243	chr2	204447164	G	A	CEU
HEM		HEM_1	HFE	rs1800562	chr6	26201120	A	G	CEU
HEM		HEM_2	HFE	rs129128	chr6	26233321	C	T	CEU
MI		MI_1	THBS4	rs1866389	chr5	79397021	G	C	CEU
MI		MI_2	9p21	rs1333049	chr9	22115503	C	G	CEU
MI		MI_3	MTHFDIL	rs6922269	chr6	151294678	A	G	CEU
MS		MS_3	DRB1						CEU
MS		MS_1	IL7R	rs6897932	chr5	35910332	C	T	CEU
MS		MS_2	IL2R	rs12722489	chr10	6142018	C	T	CEU
OA	OAK	OA_1	GDF5	rs4911178	chr20	33416034	A	G	CHB
PC		PC_5	17q12						CEU
PC		PC_1	8q24_R1	rs4242384	chr8	128587736	C	A	CEU
PC		PC_2	8q24_R3	rs6983267	chr8	128482487	G	T	CEU
PC		PC_3	8q24_R2	rs16901979	chr8	128194098	A	C	CEU
PC		PC_3	8q24_R2	rs16901979	chr8	128194098	A	C	AfrAm
PC		PC_4	TCF2	rs17765344	chr17	66618469	A	G	CEU
PS		PS_3	HLAC						CEU
PS		PS_1	IL12B	rs6859018	chr5	158669570	G	A	CEU

FIG. 25A (cont.)

Condition	Sub Type	Locus	Gene (or chr.loc on B36)	TEST SNP	B36 Chr	B36 location	Test Risk allele (plus, R)	Test Non Risk allele (plus, N)	Ethnicity/ Race-distr
PS		PS_2	IL23R	rs11209026	chr1	67478546	G	A	CEU
RA		RA_4	HLADRB1						CEU
RA		RA_5	HLADRB1						CEU
RA		RA_6	HLADRB1						CEU
RA	RA_RFpos	RA_1	PTPN22	rs6679677	chr1	114105331	A	C	CEU
RA		RA_1	PTPN22	rs6679677	chr1	114105331	A	C	CEU
RA		RA_3	PADI4	rs11203367	chr1	17530203	T	C	CEU
RA		RA_3	PADI4	rs11203367	chr1	17530203	T	C	AS
RA		RA_2	MHC	rs6452617	chr6	32771829	T	C	CEU
RLS	PLMS	RLS_3	BTBD9	rs6904723	chr6	38544295	A	C	CEU
RLS		RLS_1	MEIS1	rs2300478	chr2	66634957	G	T	CEU
RLS		RLS_2	MAP2k5_LBXCOR1	rs1026732	chr15	65882139	G	A	CEU
RLS		RLS_3	BTBD9	rs9296249	chr6	38473819	T	C	CEU
SLE		SLE_2	IRF5						CEU
SLE		SLE_3	IRF5						CEU
SLE		SLE_4	HLA DRB1						CEU
SLE		SLE_5	HLA DRB1						CEU
SLE		SLE_1	IRF5	rs12531711	chr7	128404702	G	A	CHB
T2D		T2D_12	SLC30A8						CEU
T2D		T2D_10	TCF7L2	rs4506565	chr10	114746031	T	A	CEU
T2D		T2D_11	WFS1	rs10012946	chr4	6344251	C	T	CEU
T2D		T2D_2	CDKAL1	rs7756992	chr6	20787688	G	A	CEU
T2D		T2D_2	CDKAL1	rs7756992	chr6	20787688	G	A	CHB
T2D		T2D_3	CDKN2A/B	rs10811661	chr9	22124094	T	C	CEU
T2D		T2D_4	Chr11.41871942	rs12288738	chr11	41868875	T	C	CEU
T2D		T2D_5	FTO	rs8050136	chr16	52373776	A	C	CEU

FIG. 25A (cont.)

Condition	Sub Type	Locus	Gene (or chr.loc on B36)	TEST SNP	B36 Chr	B36 location	Test Risk allele (plus, R)	Test Non Risk allele (plus, N)	Ethnicity/ Race-distr
T2D		T2D_6	HHEX	rs1111875	chr10	94452862	C	T	CEU
T2D		T2D_7	IGF2BP2	rs4402960	chr3	186994381	T	G	CEU
T2D		T2D_8	KCNJ11	rs5215	chr11	17365206	C	T	CEU
T2D		T2D_9	PPARG	rs1801282	chr3	12368125	C	G	CEU
XFG		XFG_1	LOXL1	rs2165241	chr15	72009255	T	C	CEU

FIG. 25B

Condition	Published SNP	Published Risk allele (plus)	Published Non Risk allele (plus)	UNITS for effect estimate	Effect Estimate	Genotypic risk: risk homoz (RR vs NN)	RR confidence interval
AD	rs4420638	G	A	OR (95%CI)	genotypic	17.99	8.95, 36.19
AMD	rs2230199	C	G	OR (95%CI)	genotypic	2.6	1.6, 4.1
AMD	rs1061170	C	T	OR (95%CI)	genotypic	6.3	3.8, 10.4
AMD	rs9332739	G	C	OR (95%CI)	allelic		
AMD	rs1410996	G	A	OR (95%CI)	allelic		
AMD	rs10490924	T	G	OR (95%CI)	genotypic	10.57	
AMD	rs641153	G	A	OR (95%CI)	genotypic	6.98	0.72, 67.50
BC	rs13387042	A	G	OR (95%CI)	allelic		
BC	rs3803662	A	G	OR (95%CI)	allelic		
BC	rs2981582	A	G	OR (95%CI)	genotypic	1.63	1.53, 1.72
BC	rs889312	C	A	OR (95%CI)	genotypic	1.27	1.19, 1.36
BC	rs3817198	C	T	OR (95%CI)	genotypic	1.17	1.08, 1.25
BC	rs1045485	G	C	OR (95%CI)	genotypic	1.35	1.15, 1.61
BC	rs13387042	A	G	OR (95%CI)	genotypic	1.44	1.30, 1.58
BC	rs3803662	A	G	OR (95%CI)	genotypic	1.64	1.45, 1.85
BMIOB	rs9939609	A	T	OR (95%CI)	genotypic	1.74	1.60, 1.89
BMIOB	rs9291171	G	A	OR (95%CI)	genotypic	1.53	1.12, 2.10
CD	rs2066845	C	G	OR (95%CI)	genotypic	12.13	
CD	rs5743293	C	-	OR (95%CI)	genotypic	34.66	21.79, 47.53
CD	rs10883365	G	A	OR (95%CI)	genotypic	1.62	1.37, 1.92
CD	rs17234657	G	T	OR (95%CI)	genotypic	2.32	1.59, 3.39
CD	rs10210302	T	C	OR (95%CI)	genotypic	1.85	1.56, 2.21
CD	rs9858542	A	G	OR (95%CI)	genotypic	1.84	1.49, 2.26
CD	rs11805303	T	C	OR (95%CI)	genotypic	1.86	1.54, 2.24
CD	rs1000113	T	C	OR (95%CI)	genotypic	1.92	0.92, 4.00
CD	rs17221417	G	C	OR (95%CI)	genotypic	1.92	1.58, 2.34

FIG. 25B (cont.)

Condition	Published SNP	Published Risk allele (plus)	Published Non Risk allele (plus)	UNITS for effect estimate	Effect Estimate	Genotypic risk: risk homoz (RR vs NN)	RR confidence interval
CD	rs2542151	G	T	OR (95%CI)	genotypic	2.01	1.46, 2.76
CD	rs10761659	G	A	OR (95%CI)	genotypic	1.55	1.30, 1.84
CelD	DQA1*0301 DQB1*0302	DQA1*0301 DQB1*0302	not DQA1*0301 DQB1*0302				
CelD	rs6840978	C	T	OR (95%CI)	allelic		
CelD	rs231779	T	C	OR (95%CI)	allelic		
CelD	DQA1*0501 DQB1*0201	T	C	OR (95%CI)	allelic		
CRC	rs6983267	G	T	OR (95%CI)	genotypic	1.47	1.25, 1.74
GD	DRB1*0301 DQA1*0501	DRB1*0301 DQA1*0501	not DRB1*0301 DQA1*0501	OR (95%CI)	allelic		
GD	rs3087243	G	A	OR (95%CI)	genotypic	2.32	1.71, 3.15
HEM	rs1800562	A	G		multilocus		
HEM	rs1799945	G	C		multilocus		
MI	rs1866389	G	C	OR (95%CI)	genotypic	3.07	1.32, 7.13
MI	rs10757278	G	A	OR (95%CI)	genotypic	1.72	1.45, 2.03
MI	rs6922269	A	G	OR (95%CI)	genotypic	1.53	1.28, 1.83
MS	DRB1*1501	DRB1*1501	not DRB1*1501	OR (95%CI)	genotypic	5.43	4.12, 7.16
MS	rs6897932	C	T	OR (95%CI)	genotypic	1.8	1.37, 2.35
MS	rs12722489	C	T	OR (95%CI)	genotypic	1.37	1.03, 1.80
OA	rs143383	A	G	OR (95%CI)	genotypic	2.04	1.16, 3.58
PC	rs4430796	A	G	OR (95%CI)	genotypic	1.48	1.32, 1.66
PC	rs1447295	A	C	OR (95%CI)	genotypic	2.23	1.58, 3.14
PC	rs6983267	G	T	OR (95%CI)	genotypic	1.58	1.40, 1.78
PC	rs16901979	A	C	OR (95%CI)	allelic		
PC	rs16901979	A	C	OR (95%CI)	allelic		
PC	rs1859962	G	T	OR (95%CI)	genotypic	1.45	1.29, 1.62
PS	HLAC*0602	HLAC*0602	not HLAC*0602	OR (95%CI)	allelic		
PS	rs3212227	T	G	OR (95%CI)	genotypic	2.55	1.52, 4.28

FIG. 25B (cont.)

Condition	Published SNP	Published Risk allele (plus)	Published Non Risk allele (plus)	UNITS for effect estimate	Effect Estimate	Genotypic risk: risk homoz (RR vs NN)	RR confidence interval
PS	rs11209026	G	A	OR (95% CI)	allelic		
RA	DRB1*0101	DRB1*0101	not DRB1*0101	OR (95% CI)	allelic		
RA	DRB1*0401	DRB1*0401	not DRB1*0401	OR (95% CI)	allelic		
RA	DRB1*0404	DRB1*0404	not DRB1*0404	OR (95% CI)	allelic		
RA	rs2476601	A	G	OR (95% CI)	carrier		
RA	rs2476601	A	G	OR (95% CI)	genotypic	2.26	0.56, 9.14
RA	rs2240340	T	C	OR (95% CI)	genotypic	2.1	1.66, 2.66
RA	rs2240340	T	C	OR (95% CI)	genotypic	3.19	2.52, 4.03
RA	rs6457617	T	C	OR (95% CI)	genotypic	5.21	4.31, 6.30
RLS	rs6904723	A	C	OR (95% CI)	genotypic	2.58	1.78, 3.74
RLS	rs2300478	G	T	OR (95% CI)	genotypic	3.32	2.64, 4.18
RLS	rs1026732	G	A	OR (95% CI)	genotypic	2.08	1.62, 2.66
RLS	'rs9296249	T	C	OR (95% CI)	genotypic	2.85	1.93, 4.20
SLE	rs10954213	A	G	OR (95% CI)	allelic		
SLE	rs2004640	T	G	OR (95% CI)	allelic		
SLE	DRB1*0301	DRB1*0301	not DRB1*0301	OR (95% CI)	allelic		
SLE	DRB1*0501	DRB1*1501	not DRB1*1501	OR (95% CI)	allelic		
SLE	rs2070197	C	T	OR (95% CI)	allelic		
T2D	rs13266634	C	T	OR (95% CI)	allelic		
T2D	rs4506565	T	A	OR (95% CI)	genotypic	1.88	1.56, 2.27
T2D	rs10010131	G	A	OR (95% CI)	genotypic	1.19	1.10, 1.30
T2D	rs7756992	G	A	OR (95% CI)	genotypic	1.5	1.31, 1.72
T2D	rs7756992	G	A	OR (95% CI)	genotypic	1.52	1.21, 1.90
T2D	rs10811661	T	C	OR (95% CI)	genotypic	1.39	1.13, 1.71
T2D	rs9300039	C	A	OR (95% CI)	genotypic	2.61	1.33, 5.11
T2D	rs8050136	A	C	OR (95% CI)	genotypic	1.49	1.33, 1.68

FIG. 25B (cont.)

Condition	Published SNP	Published Risk allele (plus)	Published Non Risk allele (plus)	UNITS for effect estimate	Effect Estimate	Genotypic risk: risk homoz (RR vs NN)	RR confidence interval
T2D	rs1111875	C	T	OR (95%CI)	genotypic	1.2	1.10, 1.31
T2D	rs4402960	T	G	OR (95%CI)	genotypic	1.21	1.10, 1.34
T2D	rs5219	T	C	OR (95%CI)	genotypic	1.22	1.04, 1.44
T2D	rs1801282	C	G	OR (95%CI)	genotypic	1.53	1.08, 2.16
XFG	rs2165241	T	C	OR (95%CI)	genotypic	16.54	9.40, 29.11

FIG. 25C

Condition	Genotypic risk: heteroz (RN vs NN)	RN confidence interval	Genotypic risk: nonrisk homoz (NN vs NN)	Carrier Risk (RR or RN vs NN)	RR or RN confidence interval	Allelic Risk (R vs N)	R confidence interval
AD	4.00	3.00, 5.34	1.00				
AMD	1.70	1.3, 2.1	1.00				
AMD	3.10	2.0, 4.6	1.00				
AMD						2.78	2.08, 4.76
AMD						3.16	
AMD	2.72		1.00				
AMD	2.33	0.23, 23.25	1.00				
BC						1.22	1.14, 1.31
BC						1.32	1.22, 1.42
BC	1.23	1.18, 1.28	1.00				
BC	1.13	1.09, 1.18	1.00				
BC	1.06	1.02, 1.11	1.00				
BC	1.12	1.06, 1.18	1.00				
BC	1.11	1.03, 1.20	1.00			1.2	1.14, 1.26
BC	1.27	1.19, 1.36	1.00			1.28	1.21, 1.35
BMIOB	1.31	1.23, 1.39	1.00				
BMIOB	1.24	1.04, 1.47	1.00				
CD	3.05						
CD	4.55	3.21, 5.89					
CD	1.20	1.03, 1.39	1.00				
CD	1.54	1.34, 1.76	1.00				
CD	1.19	1.01, 1.41	1.00				
CD	1.09	0.96, 1.24	1.00				
CD	1.39	1.22, 1.58	1.00				
CD	1.54	1.31, 1.82	1.00				
CD	1.29	1.13, 1.46	1.00				

FIG. 25C (cont.)

Condition	Genotypic risk: heteroz (RN vs NN)	RN confidence interval	Genotypic risk: nonrisk homoz (NN vs NN)	Carrier Risk (RR or RN vs NN)	RR or RN confidence interval	Allelic Risk (R vs N)	R confidence interval
CD	1.30	1.13, 1.48	1.00				
CD	1.23	1.05, 1.45	1.00				
CelD							
CelD						1.42	1.28, 1.59
CelD						1.24	1.04, 1.49
CelD						7.04	6.08, 8.15
CRC	1.04	0.90, 1.20	1				
GD						2.72	1.91, 3.87
GD	1.59	1.19, 2.13	1				
HEM							
HEM							
MI	1.16	0.78, 1.73	1.00				
MI	1.28	1.14, 1.45	1.00				
MI	1.23	1.11, 1.36	1				
MS	2.92	2.42, 3.51	1				
MS	1.46	1.11, 1.92	1				
MS	1.06	0.80, 1.41	1				
OA	1.27	0.71, 2.28	1.00				
PC	1.24	1.13, 1.36	1.00				
PC	1.43	1.29, 1.59	1.00				
PC	1.26	1.13, 1.41	1.00				
PC						1.79	1.53, 2.11
PC						1.34	1.09, 1.64
PC	1.33	1.21, 1.44	1.00				
PS						3.1	2.37, 4.08
PS	1.47	0.86, 2.5	1				

FIG. 25C (cont.)

Condition	Genotypic risk: heteroz (RN vs NN)	RN confidence interval	Genotypic risk: nonrisk homoz (NN vs NN)	Carrier Risk (RR or RN vs NN)	RR or RN confidence interval	Allelic Risk (R vs N)	R confidence interval
PS						1.59	1.27, 2.00
RA						1.1	
RA						6.1	
RA						4.6	
RA				1.71	1.25, 2.34		
RA	1.69	1.23, 2.32	1.00				
RA	1.12	0.91, 1.98	1				
RA	1.32	1.14, 1.53	1				
RA	2.36	1.97, 2.84	1.00				
RLS	1.86	1.30, 2.67	1				
RLS	1.82	1.59, 2.09	1				
RLS	1.44	1.12, 1.86	1				
RLS	1.67	1.45, 1.92	1				
SLE						1.44	1.14, 1.81
SLE						1.62	1.30, 2.01
SLE						2	1.6, 2.4
SLE						1.4	1.2, 1.7
SLE						2.04	1.52, 2.74
T2D						1.18	1.09, 1.29
T2D	1.36	1.20, 1.54	1.00				
T2D	1.03	0.95, 1.12	1				
T2D	1.15	1.06, 1.24	1.00				
T2D	1.27	1.05, 1.55	1.00				
T2D	1.16	0.94, 1.43	1.00				
T2D	1.80	0.91, 3.57	1.00				
T2D	1.15	1.06, 1.26	1.00				

FIG. 25C (cont.)

Condition	Genotypic risk: heteroz (RN vs NN)	RN confidence interval	Genotypic risk: nonrisk homoz (NN vs NN)	Carrier Risk (RR or RN vs NN)	RR or RN confidence interval	Allelic Risk (R vs N)	R confidence interval
T2D	1.06	0.98, 1.16	1.00				
T2D	1.16	1.09, 1.24	1.00				
T2D	1.12	0.98, 1.28	1.00				
T2D	1.30	0.91, 1.86	1.00				
XFG	3.72	2.07, 6.68	1				

FIG. 25D

Condition	Seminal publication	Direct or tag snp	Published SNP B36 Chr	Published SNP B36 location	Published Minor allele (plus)	Published Major allele (plus)
AD	Coon, J Clin Psychiatry 68:4. 2007	TAG	chr19	50114786	G	A
AMD	Yates, NEJM 357:553. 2007		chr11	6669387	C	G
AMD	Yates, NEJM 357:553. 2007		chr1	194925860	C	T
AMD	Gold. Nat Genet 38:45. 2006		chr6	32011783	C	G
AMD	Maller. NatGen 38:1055. 2007	TAG	chr1	194963556	A	G
AMD	Jakobsdottir. AJHG 77:389. 2005	DIRECT	chr10	124204438	T	G
AMD	Gold. Nat Genet 38:45. 2006	TAG	chr6	32022159	A	G
BC	Stacey. NatGen 39:865. 2007	TAG	chr2	217614077	G	A
BC	Stacey. NatGen 39:865. 2007	DIRECT	chr16	51143842	A	G
BC	Easton. Nature 447:1087. 2007	DIRECT	chr10	123342307	A	G
BC	Easton. Nature 447:1087. 2007	TAG	chr5	56067641	C	A
BC	Easton. Nature 447:1087. 2007	DIRECT	chr11	1865582	C	T
BC	Cox. NatGen 39:352. 2007	TAG	chr2	201857834	C	G
BC	Stacey. NatGen 39:865. 2007	TAG	chr2	217614077	G	A
BC	Stacey. NatGen 39:865. 2007	DIRECT	chr6	51143842	A	G
BMIOB	Frayling. Science 316:889. 2007	DIRECT	chr16	52378028	A	T
BMIOB	Dahlman. AJHG 80:1115. 2007	DIRECT	chr4	73200490	G	A
CD	Pascoe. EJHG 15:864. 2007		chr16	49314041	C	G
CD	Pascoe. EJHG 15:864. 2007		chr16	49321283	C	-
CD	WTCCC. NATURE 447:661. 2007	DIRECT	chr10	101277754	G	A
CD	WTCCC. NATURE 447:661. 2007	DIRECT	chr5	40437266	G	T
CD	WTCCC. NATURE 447:661. 2007	DIRECT	chr2	233823578	C	T
CD	WTCCC. NATURE 447:661. 2007	DIRECT	chr3	49676987	A	G
CD	WTCCC. NATURE 447:661. 2007	DIRECT	chr1	67448104	T	C
CD	WTCCC. NATURE 447:661. 2007	DIRECT	chr5	150220269	T	C
CD	WTCCC. NATURE 447:661. 2007	TAG	chr16	49297083	G	C

FIG. 25D (cont.)

Condition	Seminal publication	Direct or tag snp	Published SNP B36 Chr	Published SNP B36 location	Published Minor allele (plus)	Published Major allele (plus)
CD	WTCCC. Nature 447:661. 2007	DIRECT	chr18	12769947	G	T
CD	WTCCC. Nature 447:661. 2007	DIRECT	chr10	64115570	A	G
CelD			chr6			
CelD	van Heel. Nat Genet 39:827. 2007	DIRECT	chr4	123774157	T	C
CelD	Hunt. EJHG 13:440. 2005; van Heel Nat Genet 39:827. 2007	TAG	chr2	204442732	T	C
CelD	van Heel Nat Genet 39:827. 2007	TAG	chr6		T	C
CRC	Haiman, NatGen July 8, 2007	DIRECT	chr8	128482487	G	T
GD	Heward. J Clin Endocr Metab 83:3394, 1998.		chr6			
GD	Ueda. Nature 423:506. 2003	DIRECT	chr2	204447164	A	G
HEM	Burke, Gen Med 2:271. 2000	DIRECT	chr6	26201120	A	G
HEM	Burke, Gen Med 2:271. 2000	TAG	chr6	26199158	G	C
MI	Wessel. AHJ 147:905. 2004	DIRECT	chr5	79397021	C	G
MI	Helgadottir. Science 316:1491. 2007	TAG	chr9	22114477	G	A
MI	Samani. NEJM July 2007	DIRECT	chr6	151294678	A	G
MS	Ramagopalan. PlosGen 3:1607. 2007		chr6			
MS	Gregory. NatGen AOP 7/29/07	DIRECT	chr5	35910332	T	C
MS	Intl MS Cons. NEJM 7/29/07	DIRECT	chr10	6142018	T	C
OA	Miyamoto. NatGen 39:539. 2007	TAG	chr20	33489397	G	A
PC	Gudmundsson. NatGen 39:977. 2007		chr17	33172153	A	G
PC	Yeagar. NatGen 39:645. 2007	TAG	chr8	128554220	A	C
PC	Yeagar. NatGen 39:645. 2007	DIRECT	chr8	128482487	G	T
PC	Gudmundsson. NatGen 39:631. 2007	DIRECT	chr8	128194098	A	C
PC	Gudmundsson. NatGen 39:631. 2007	DIRECT	chr8	128194098	A	C
PC	Gudmundsson. NatGen 39:977. 2007	TAG	chr17	66620348	G	T
PS	Cargill. AJHG 80:273. 2007		chr6			
PS	Cargill. AJHG 80:273. 2007	TAG	chr5	158675528	G	T

FIG. 25D (cont.)

Condition	Seminal publication	Direct or tag snp	Published SNP B36 Chr	Published SNP B36 location	Published Minor allele (plus)	Published Major allele (plus)
PS	Cargill. AJHG 80:273. 2007	DIRECT	chr1	67478546	A	G
RA	The Genetic Basis of Common Diseases, 2ed. Ed: R. King, J. Rotter, A. Motulsky, 2002		chr6			
RA	The Genetic Basis of Common Diseases, 2ed. Ed: R. King, J. Rotter, A. Motulsky, 2002		chr6			
RA	The Genetic Basis of Common Diseases, 2ed. Ed: R. King, J. Rotter, A. Motulsky, 2002		chr6			
RA	Begovich. AJHG. 75:330, 2004	TAG	chr1	114179091	A	G
RA	Begovich. AJHG. 75:330. 2004	TAG	chr1	114179091	A	G
RA	Lee, Rheumlot 27:827. 2007	TAG	chr1	17535226	T	C
RA	Lee, Rheumlot 27:827. 2007	TAG	chr1	17535226	T	C
RA	WTCCC. Nature 447:661. 2007	TAG			T	C
RLS	Stefansson. NEIM 357. July 18, 2007	DIRECT	chr6	38544295	C	A
RLS	Winkelman. Nat Genet July 2007	DIRECT	chr2	66634957	G	T
RLS	Winkelman. Nat Genet July 2007	DIRECT	chr15	65882139	A	G
RLS	Winkelman. Nat Genet July 2007	DIRECT	chr6	38473819	C	T
SLE	Graham. PNAS 104:6758. 2007		chr7	128376663	G	A
SLE	Graham. PNAS 104:6758. 2007		chr7	128365537	G	T
SLE	Graham. EJHG 15:823. 2007		chr6			
SLE	Graham. EJHG 15:823. 2007		chr6			
SLE	Graham. PNAS 104:6758. 2007	TAG	chr7	128376236	C	T
T2D	Scott. Science 316:1341. 2007		chr8	118253964	T	C
T2D	WTCCC. Nature 447:661. 2007	DIRECT	chr10	114746031	T	A
T2D	Sandhu. NatGen July 1, 2007	TAG	chr4	6343816	A	G
T2D	Steinthorsdottir. Nat Genet 39:770. 2007	DIRECT	chr6	20787688	G	A

FIG. 25D (cont.)

Condition	Seminal publication	Direct or tag snp	Published SNP B36 Chr	Published SNP B36 location	Published Minor allele (plus)	Published Major allele (plus)
T2D	Steinthorsdottir. Nat Genet 39:770. 2007	DIRECT	ch6r	20787688	G	A
T2D	Scott. Science 316:1341. 2007; Zeggini. Science 316:1336.2007	DIRECT	chr9	22124094	C	T
T2D	Scott. Science 316:1341. 2007	TAG	chr11	41871942	A	C
T2D	Zeggini. Science 316:1336.2007	DIRECT	chr16	52373776	A	C
T2D	Scott. Science 316:1341. 2007	DIRECT	chr10	94452862	T	C
T2D	Scott. Science 316:1341. 2007	DIRECT	chr3	186994381	T	G
T2D	Scott. Science 316:1341. 2007	TAG	chr11	17366148	T	C
T2D	Scott. Science 316:1341. 2007	DIRECT	chr3	12368125	G	C
XFG	Thorleifsson. Science Express Aug 9, 2007	DIRECT	chr15	72009255	T	C

GENETIC ANALYSIS SYSTEMS AND METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a U.S. National Stage (§371) entry of International Application No. PCT/US07/86138 filed Nov. 30, 2007 which claims priority to U.S. Provisional Application No. 60/868,066 filed Nov. 30, 2006 and to U.S. Provisional Application No. 60/951,123 filed Jul. 20, 2007 and to U.S. Provisional Application No. 60/972,198 filed Sep. 13, 2007 and to U.S. Provisional Application No. 60/985,622 filed Nov. 5, 2007 and to U.S. Provisional Application No. 60/989,685 filed Nov. 21, 2007 and a Continuation to U.S. application Ser. No. 11/781,679, filed Jul. 23, 2007 now abandoned which claims priority to U.S. Provisional Application No. 60/868,066 filed Nov. 30, 2006 and to U.S. Provisional Application No. 60/951,123 filed Jul. 20, 2007, which disclosures are herein incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

Sequencing of the human genome and other recent developments in human genomics has revealed that the genomic makeup between any two humans has over 99.9% similarity. The relatively small number of variations in DNA between individuals gives rise to differences in phenotypic traits, and is related to many human diseases, susceptibility to various diseases, and response to treatment of disease. Variations in DNA between individuals occur in both coding and noncoding regions, and include changes in bases at a particular locus in genomic DNA sequences, as well as insertions and deletions of DNA. Changes that occur at single base positions in the genome are referred to as single nucleotide polymorphisms, or "SNPs."

While SNPs are relatively rare in the human genome, they account for a majority of DNA sequence variations between individuals, occurring approximately once every 1,200 base pairs in the human genome (see International HapMap Project, www.hapmap.org). As more human genetic information becomes available, the complexity of SNPs is beginning to be understood. In turn, the occurrences of SNPs in the genome are becoming correlated to the presence of and/or susceptibility to various diseases and conditions.

As these correlations and other advances in human genetics are being made, medicine and personal health in general are moving toward a customized approach in which a patient will make appropriate medical and other choices in consideration of his or her genomic information, among other factors. Thus, there is a need to provide individuals and their caregivers with information specific to the individual's personal genome toward providing personalized medical and other decisions.

SUMMARY OF THE INVENTION

The present invention provides a method of assessing an individual's genotype correlations comprising: a) obtaining a genetic sample of the individual, b) generating a genomic profile for the individual, c) determining the individual's genotype correlations with phenotypes by comparing the individual's genomic profile to a current database of human genotype correlations with phenotypes, d) reporting the results from step c) to the individual or a health care manager of the individual, e) updating the database of human genotype correlations with an additional human genotype correlation as the additional human genotype correlation becomes known, f) updating the individual's genotype correlations by comparing the individual's genomic profile from step c) or a portion thereof to the additional human genotype correlation and determining an additional genotype correlation of the individual, and g) reporting the results from step f) to the individual or the health care manager of the individual.

The present invention further provides a business method of assessing genotype correlations of an individual comprising: a) obtaining a genetic sample of the individual; b) generating a genomic profile for the individual; c) determining the individual's genotype correlations by comparing the individual's genomic profile to a database of human genotype correlations; d) providing results of the determining of the individual's genotype correlations to the individual in a secure manner; e) updating the database of human genotype correlations with an additional human genotype correlation as the additional human genotype correlation becomes known; f) updating the individual's genotype correlations by comparing the individual's genomic profile or a portion thereof to the additional human genotype correlation and determining an additional genotype correlation of the individual; and g) providing results of the updating of the individual's genotype correlations to the individual of the health care manager of the individual.

Another aspect of the present invention is a method generating a phenotype profile for an individual comprising: a) providing a rule set comprising rules, each rule indicating a correlation between at least one genotype and at least one phenotype, b) providing a data set comprising genomic profiles of each of a plurality of individuals, wherein each genomic profile comprises a plurality of genotypes; c) periodically updating the rule set with at least one new rule, wherein the at least one new rule indicates a correlation between a genotype and a phenotype not previously correlated with each other in the rule set; d) applying each new rule to the genomic profile of at least one of the individuals, thereby correlating at least one genotype with at least one phenotype for the individual, and optionally, e) generating a report comprising the phenotype profile of the individual.

The present invention also provides a system comprising a) a rule set comprising rules, each rule indicating a correlation between at least one genotype and at least one phenotype; b) code that periodically updates the rule set with at least one new rule, wherein the at least one new rule indicates a correlation between a genotype and a phenotype not previously correlated with each other in the rule set; c) a database comprising genomic profiles of a plurality of individuals; d) code that applies the rule set to the genomic profiles of individuals to determine phenotype profiles for the individuals; and e) code that generates reports for each individual.

Another aspect of the present invention is transmission over a network, in a secure or non-secure manner, the methods and systems described above.

INCORPORATION BY REFERENCE

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a flow chart illustrating aspects of the method herein.

FIG. **2** is an example of a genomic DNA quality control measure.

FIG. **3** is an example of a hybridization quality control measure.

FIG. **4** are tables of representative genotype correlations from published literature with test SNPs and effect estimates. A-I) represents single locus genotype correlations; J) represents a two locus genotype correlation; K) represents a three locus genotype correlation; L) is an index of the ethnicity and country abbreviations used in A-K; M) is an index of the abbreviations of the Short Phenotype Names in A-K, the heritability, and the references for the heritability.

FIG. **5**A-J are tables of representative genotype correlations with effect estimates.

FIG. **6**A-F are tables of representative genotype correlations and estimated relative risks.

FIG. **7** is a sample report.

FIG. **8** is a schematic of a system for the analysis and transmission of genomic and phenotype profiles over a network.

FIG. **9** is a flow chart illustrating aspects of the business method herein

FIG. **10**: The effect of the estimate of the prevalence on the relative risk estimations. Each of the plots correspond to a different value of the allele frequencies in the populations, assuming Hardy-Weinberg Equilibrium. The two black lines correspond to odds ratio of 9 and 6, the two red lines correspond to 6 and 4, and the two blue lines correspond to odds ratio of 3 and 2.

FIG. **11**: The effect of the estimate of the allele frequencies on the relative risk estimations. Each of the plots correspond to a different value of the prevalence in the populations. The two black lines correspond to odds ratio of 9 and 6, the two red lines correspond to 6 and 4, and the two blue lines correspond to odds ratio of 3 and 2.

FIG. **12**: Pairwise Comparison of the absolute values of the different models

FIG. **13**: Pairwise Comparison of the ranked values (GCI scores) based on the different models. The Spearman correlations between the different pairs are given in Table 2.

FIG. **14**: Effect of Prevalence Reporting on the GCI score. The Spearman correlation between any two prevalence values is at least 0.99.

FIG. **15**: are illustrations of sample webpages from a personalized portal.

FIG. **16**: are illustrations of sample webpages from a personalized portal for a person's risk for prostate cancer.

FIG. **17**: are illustrations of sample webpages from a personalized portal for an individual's risk for Crohn's disease.

FIG. **18**: is a histogram of GCI scores for Multiple Sclerosis based on the HapMAP using 2 SNPs.

FIG. **19**: is an individuals' lifetime risk for Multiple Sclerosis using GCI Plus.

FIG. **20**: is a histogram of GCI scores for Crohn's disease.

FIG. **21**: is a table of multilocus correlations.

FIG. **22**: is a table of SNPs and phenotype correlations.

FIG. **23**: is a table of phenotypes and prevalences.

FIG. **24**: is a glossary for abbreviations in FIGS. **21**, **22**, and **25**.

FIG. **25**: is a table of SNPs and phenotype correlations.

DETAILED DESCRIPTION

The present invention provides methods and systems for generating phenotype profiles based on a stored genomic profile of an individual or group of individuals, and for readily generating original and updated phenotype profiles based on the stored genomic profiles. Genomic profiles are generated by determining genotypes from biological samples obtained from individuals. Biological samples obtained from individuals may be any sample from which a genetic sample may be derived. Samples may be from buccal swabs, saliva, blood, hair, or any other type of tissue sample. Genotypes may then be determined from the biological samples. Genotypes may be any genetic variant or biological marker, for example, single nucleotide polymorphisms (SNPs), haplotypes, or sequences of the genome. The genotype may be the entire genomic sequence of an individual. The genotypes may result from high-throughput analysis that generates thousands or millions of data points, for example, microarray analysis for most or all of the known SNPs. In other embodiments, genotypes may also be determined by high throughput sequencing.

The genotypes form a genomic profile for an individual. The genomic profile is stored digitally and is readily accessed at any point of time to generate phenotype profiles. Phenotype profiles are generated by applying rules that correlate or associate genotypes with phenotypes. Rules can be made based on scientific research that demonstrates a correlation between a genotype and a phenotype. The correlations may be curated or validated by a committee of one or more experts. By applying the rules to a genomic profile of an individual, the association between an individual's genotype and a phenotype may be determined. The phenotype profile for an individual will have this determination. The determination may be a positive association between an individual's genotype and a given phenotype, such that the individual has the given phenotype, or will develop the phenotype. Alternatively, it may be determined that the individual does not have, or will not develop, a given phenotype. In other embodiments, the determination may be a risk factor, estimate, or a probability that an individual has, or will develop a phenotype.

The determinations may be made based on a number of rules, for example, a plurality of rules may be applied to a genomic profile to determine the association of an individual's genotype with a specific phenotype. The determinations may also incorporate factors that are specific to an individual, such as ethnicity, gender, lifestyle (for example, diet and exercise habits), age, environment (for example, location of residence), family medical history, personal medical history, and other known phenotypes. The incorporation of the specific factors may be by modifying existing rules to encompass these factors. Alternatively, separate rules may be generated by these factors and applied to a phenotype determination for an individual after an existing rule has been applied.

Phenotypes may include any measurable trait or characteristic, such as susceptibility to a certain disease or response to a drug treatment. Other phenotypes that may be included are physical and mental traits, such as height, weight, hair color, eye color, sunburn susceptibility, size, memory, intelligence, level of optimism, and general disposition. Phenotypes may also include genetic comparisons to other individuals or organisms. For example, an individual may be interested in the similarity between their genomic profile and that of a celebrity. They may also have their genomic profile compared to other organisms such as bacteria, plants, or other animals.

Together, the collection of correlated phenotypes determined for an individual comprises the phenotype profile for the individual. The phenotype profile may be accessible by an on-line portal. Alternatively, the phenotype profile as it exists at a certain time may be provided in paper form, with subsequent updates also provided in paper form. The phenotype profile may also be provided by an on-line portal. The on-line portal may optionally be a secure on-line portal. Access to the phenotype profile may be provided to a subscriber, which is an individual who subscribes to the service that generates rules on correlations between phenotypes and genotypes, determines the genomic profile of an individual, applies the rules to the genomic profile, and generates a phenotype profile of the individual. Access may also be provided to non-subscribers, wherein they may have limited access to their phenotype profile and/or reports, or may have an initial report or phenotype profile generated, but updated reports will be generated only with purchase of a subscription. Health care managers and providers, such as caregivers, physicians, and genetic counselors may also have access to the phenotype profile.

In another aspect of the invention a genomic profile may be generated for subscribers and non-subscribers and stored digitally but access to the phenotype profile and reports may be limited to subscribers. In another variation, both subscribers and non-subscribers may access their genotype and phenotype profiles, but have limited access, or have a limited report generated for non-subscribers, whereas subscribers have full access and may have a full report generated. In another embodiment, both subscribers and non-subscribers may have full access initially, or full initial reports, but only subscribers may access updated reports based on their stored genomic profile.

In another aspect of the invention information about the association of multiple genetic markers with one or more diseases or conditions is combined and analyzed to produce a Genetic Composite Index (GCI) score. This score incorporates known risk factors, as well as other information and assumptions such as the allele frequencies and the prevalence of a disease. The GCI can be used to qualitatively estimate the association of a disease or a condition with the combined effect of a set of Genetic markers. The GCI score can be used to provide people not trained in genetics with a reliable (i.e., robust), understandable, and/or intuitive sense of what their individual risk of a disease is compared to a relevant population based on current scientific research. The GCI score may be used to generate GCI Plus scores. The GCI Plus score may contain all the GCI assumptions, including risk (such as lifetime risk), age-defined prevalence, and/or age-defined incidence of the condition. The lifetime risk for the individual may then be calculated as a GCI Plus score which is proportional to the individual's GCI score divided by the average GCI score. The average GCI score may be determined from a group of individuals of similar ancestral background, for example a group of Caucasians, Asians, East Indians, or other group with a common ancestral background. Groups may comprise of at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, or 60 individuals. In some embodiments, the average may be determined from at least 75, 80, 95, or 100 individuals. The GCI Plus score may be determined by determining the GCI score for an individual, dividing the GCI score by the average relative risk and multiplying by the lifetime risk for a condition or phenotype. For example, using data from FIG. **22** and/or FIG. **25** with information in FIG. **24** to calculate GCI Plus scores such as in FIG. **19**.

The present invention encompasses using the GCI score as described herein, and one of ordinary skill in the art will readily recognize the use of GCI Plus scores or variations thereof, in place of GCI scores as described herein.

In one embodiment a GCI score is generated for each disease or condition of interest. These GCI scores may be collected to form a risk profile for an individual. The GCI scores may be stored digitally so that they are readily accessible at any point of time to generate risk profiles. Risk profiles may be broken down by broad disease classes, such as cancer, heart disease, metabolic disorders, psychiatric disorders, bone disease, or age on-set disorders. Broad disease classes may be further broken down into subcategories. For example for a broad class such as a cancer, sub-categories of cancer may be listed such as by type (sarcoma, carcinoma or leukemia, etc.) or by tissue specificity (neural, breast, ovaries, testes, prostate, bone, lymph nodes, pancreas, esophagus, stomach, liver, brain, lung, kidneys, etc.).

In another embodiment a GCI score is generated for an individual, which provides them with easily comprehended information about the individual's risk of acquiring or susceptibility to at least one disease or condition. In one embodiment multiple GCI scores are generated for different diseases or conditions. In another embodiment at least one GCI score is accessible by an on-line portal. Alternatively, at least one GCI score may be provided in paper form, with subsequent updates also provided in paper form. In one embodiment access to at least one GCI score is provided to a subscriber, which is an individual who subscribes to the service. In an alternative embodiment access is provided to non-subscribers, wherein they may have limited access to at least one of their GCI scores, or they may have an initial report on at least one of their GCI scores generated, but updated reports will be generated only with purchase of a subscription. In another embodiment health care managers and providers, such as caregivers, physicians, and genetic counselors may also have access to at least one of an individual's GCI scores.

There may also be a basic subscription model. A basic subscription may provide a phenotype profile where the subscriber may choose to apply all existing rules to their genomic profile, or a subset of the existing rules, to their genomic profile. For example, they may choose to apply only the rules for disease phenotypes that are actionable. The basic subscription may have different levels within the subscription class. For example, different levels may be dependent on the number of phenotypes a subscriber wants correlated to their genomic profile, or the number of people that may access their phenotype profile. Another level of basic subscription may be to incorporate factors specific to an individual, such as already known phenotypes such as age, gender, or medical history, to their phenotype profile. Still another level of the basic subscription may allow an individual to generate at least one GCI score for a disease or condition. A variation of this level may further allow an individual to specify for an automatic update of at least one GCI score for a disease or condition to be generated if their is any change in at least one GCI score due to changes in the analysis used to generate at least one GCI score. In some embodiments the individual may be notified of the automatic update by email, voice message, text message, mail delivery, or fax.

Subscribers may also generate reports that have their phenotype profile as well as information about the phenotypes, such as genetic and medical information about the phenotype. For example, the prevalence of the phenotype in the population, the genetic variant that was used for the correlation, the molecular mechanism that causes the phenotype, therapies for the phenotype, treatment options for the phenotype, and preventative actions, may be included in the report. In other embodiments, the reports may also include information such as the similarity between an individual's genotype and that of other individuals, such as celebrities or other famous people. The information on similarity may be, but are not limited to, percentage homology, number of identical variants, and phenotypes that may be similar. These reports may further contain at least one GCI score.

The report may also provide links to other sites with further information on the phenotypes, links to on-line support groups and message boards of people with the same phenotype or one or more similar phenotypes, links to an on-line genetic counselor or physician, or links to schedule telephonic or in-person appointments with a genetic counselor or physician, if the report is accessed on-line. If the report is in paper form, the information may be the website location of the aforementioned links, or the telephone number and address of the genetic counselor or physician. The subscriber may also choose which phenotypes to include in their phenotype profile and what information to include in their report. The phenotype profile and reports may also be accessible by an individual's health care manager or provider, such as a caregiver, physician, psychiatrist, psychologist, therapist, or genetic counselor. The subscriber may be able to choose whether the phenotype profile and reports, or portions thereof, are accessible by such individual's health care manager or provider.

The present invention may also include a premium level of subscription. The premium level of subscription maintains their genomic profile digitally after generation of an initial phenotype profile and report, and provides subscribers the opportunity to generate phenotype profiles and reports with updated correlations from the latest research. In another embodiment, subscribers have the opportunity to generate risk profile and reports with updated correlations from the latest research. As research reveals new correlations between genotypes and phenotypes, disease or conditions, new rules will be developed based on these new correlations and can be applied to the genomic profile that is already stored and being maintained. The new rules may correlate genotypes not previously correlated with any phenotype, correlate genotypes with new phenotypes, modify existing correlations, or provide the basis for adjustment of a GCI score based on a newly discovered association between a genotype and disease or condition. Subscribers may be informed of new correlations via e-mail or other electronic means, and if the phenotype is of interest, they may choose to update their phenotype profile with the new correlation. Subscribers may choose a subscription where they pay for each update, for a number of updates or an unlimited number of updates for a designated time period (e.g. three months, six months, or one year). Another subscription level may be where a subscriber has their phenotype profile or risk profile automatically updated, instead of where the individual chooses when to update their phenotype profile or risk profile, whenever a new rule is generated based on a new correlation.

In another aspect of the subscription, subscribers may refer non-subscribers to the service that generates rules on correlations between phenotypes and genotypes, determines the genomic profile of an individual, applies the rules to the genomic profile, and generates a phenotype profile of the individual. Referral by a subscriber may give the subscriber a reduced price on subscription to the service, or upgrades to their existing subscriptions. Referred individuals may have free access for a limited time or have a discounted subscription price.

Phenotype profiles and reports as well as risk profiles and reports may be generated for individuals that are human and non-human. For example, individuals may include other mammals, such as bovines, equines, ovines, canines, or felines. Subscribers, as used herein, are human individuals who subscribe to a service by purchase or payment for one or more services. Services may include, but are not limited to, one or more of the following: having their or another individual's, such as the subscriber's child or pet, genomic profile determined, obtaining a phenotype profile, having the phenotype profile updated, and obtaining reports based on their genomic and phenotype profile.

In another aspect of the invention, "field-deployed" mechanisms may be gathered from individuals to generate phenotype profiles for individuals. In preferred embodiments, an individual may have an initial phenotype profile generated based on genetic information. For example, an initial phenotype profile is generated that includes risk factors for different phenotypes as well as suggested treatments or preventative measures. For example, the profile may include information on available medication for a certain condition, and/or suggestions on dietary changes or exercise regimens. The individual may choose to see, or contact via a web portal or phone call, a physician or genetic counselor, to discuss their phenotype profile. The individual may decide to take a certain course of action, for example, take specific medications, change their diet, etc.

The individual may then subsequently submit biological samples to assess changes in their physical condition and possible change in risk factors. Individuals may have the changes determined by directly submitting biological samples to the facility (or associated facility, such as a facility contracted by the entity generating the genetic profiles and phenotype profiles us) that generates the genomic profiles and phenotype profiles. Alternatively, the individuals may use a "field-deployed" mechanism, wherein the individual may submit their saliva, blood, or other biological sample into a detection device at their home, analyzed by a third party, and the data transmitted to be incorporated into another phenotype profile. For example, an individual may have received an initial phenotype report based on their genetic data reporting the individual having an increased lifetime risk of myocardial infarction (MI). The report may also have suggestions on preventative measures to reduce the risk of MI, such as cholesterol lowering drugs and change in diet. The individual may choose to contact a genetic counselor or physician to discuss the report and the preventative measures and decides to change their diet. After a period of being on the new diet, the individual may see their personal physician to have their cholesterol level measured. The new information (cholesterol level) may be transmitted (for example, via the Internet) to the entity with the genomic information, and the new information used to generate a new phenotype profile for the individual, with a new risk factor for myocardial infarction, and/or other conditions.

The individual may also use a "field-deployed" mechanism, or direct mechanism, to determine their individual response to specific medications. For example, an individual may have their response to a drug measured, and the information may be used to determine more effective treatments. Measurable information include, but are not limited to, metabolite levels, glucose levels, ion levels (for example, calcium, sodium, potassium, iron), vitamins, blood cell counts, body mass index (BMI), protein levels, transcript levels, heart rate, etc., can be determined by methods readily available and can be factored into an algorithm to combine with initial genomic profiles to determine a modified overall risk estimate score.

The term "biological sample" refers to any biological sample that can be isolated from an individual, including samples from which genetic material may be isolated. As used herein, a "genetic sample" refers to DNA and/or RNA obtained or derived from an individual.

As used herein, the term "genome" is intended to mean the full complement of chromosomal DNA found within the nucleus of a human cell. The term "genomic DNA" refers to one or more chromosomal DNA molecules occurring naturally in the nucleus of a human cell, or a portion of the chromosomal DNA molecules.

The term "genomic profile" refers to a set of information about an individual's genes, such as the presence or absence of specific SNPs or mutations. Genomic profiles include the genotypes of individuals. Genomic profiles may also be substantially the complete genomic sequence of an individual. In some embodiments, the genomic profile may be at least 60%, 80%, or 95% of the complete genomic sequence of an individual. The genomic profile may be approximately 100% of the complete genomic sequence of an individual. In reference to a genomic profile, "a portion thereof" refers to the genomic profile of a subset of the genomic profile of an entire genome.

The term "genotype" refers to the specific genetic makeup of an individual's DNA. The genotype may include the genetic variants and markers of an individual. Genetic markers and variants may include nucleotide repeats, nucleotide insertions, nucleotide deletions, chromosomal translocations, chromosomal duplications, or copy number variations. Copy number variation may include microsatellite repeats, nucleotide repeats, centromeric repeats, or telomeric repeats. The genotypes may also be SNPs, haplotypes, or diplotypes. A haplotype may refer to a locus or an allele. A haplotype is also referred to as a set of single nucleotide polymorphisms (SNPs) on a single chromatid that are statistically associated. A diplotype is a set of haplotypes.

The term single nucleotide polymorphism or "SNP" refers to a particular locus on a chromosome which exhibits variability such as at least one percent (1%) with respect to the identity of the nitrogenous base present at such locus within the human population For example, where one individual might have adenosine (A) at a particular nucleotide position of a given gene, another might have cytosine (C), guanine (G), or thymine (T) at this position, such that there is a SNP at that particular position.

As used herein, the terminology "SNP genomic profile" refers to the base content of a given individual's DNA at SNP sites throughout the individual's entire genomic DNA sequence. A "SNP profile" can refer to an entire genomic profile, or may refer to a portion thereof, such as a more localized SNP profile which can be associated with a particular gene or set of genes.

The term "phenotype" is used to describe a quantitative trait or characteristic of an individual. Phenotypes include, but are not limited to, medical and non-medical conditions. Medical conditions include diseases and disorders. Phenotypes may also include physical traits, such as hair color, physiological traits, such as lung capacity, mental traits, such as memory retention, emotional traits, such as ability to control anger, ethnicity, such as ethnic background, ancestry, such as an individual's place of origin, and age, such as age expectancy or age of onset of different phenotypes. Phenotypes may also be monogenic, wherein it is thought that one gene may be correlated with a phenotype, or multigenic, wherein more than one gene is correlated with a phenotype.

A "rule" is used to define the correlation between a genotype and a phenotype. The rules may define the correlations by a numerical value, for example by a percentage, risk factor, or confidence score. A rule may incorporate the correlations of a plurality of genotypes with a phenotype. A "rule set" comprises more than one rule. A "new rule" may be a rule that indicates a correlation between a genotype and a phenotype for which a rule does not currently exist. A new rule may correlate an uncorrelated genotype with a phenotype. A new rule may also correlate a genotype that is already correlated with a phenotype to a phenotype it had not been previously correlated to. A "new rule" may also be an existing rule that is modified by other factors, including another rule. An existing rule may be modified due to an individual's known characteristics, such as ethnicity, ancestry, geography, gender, age, family history, or other previously determined phenotypes.

Use of "genotype correlation" herein refers to the statistical correlation between an individual's genotype, such as presence of a certain mutation or mutations, and the likelihood of being predisposed to a phenotype, such as a particular disease, condition, physical state, and/or mental state. The frequency with which a certain phenotype is observed in the presence of a specific genotype determines the degree of genotype correlation or likelihood of a particular phenotype. For example, as detailed herein, SNPs giving rise to the apolipoprotein E4 isoform are correlated with being predisposed to early onset Alzheimer's disease. Genotype correlations may also refer to correlations wherein there is not a predisposition to a phenotype, or a negative correlation. The genotype correlations may also represent an estimate of an individual to have a phenotype or be predisposed to have a phenotype. The genotype correlation may be indicated by a numerical value, such as a percentage, a relative risk factor, an effects estimate, or confidence score.

The term "phenotype profile" refers to a collection of a plurality of phenotypes correlated with a genotype or genotypes of an individual. Phenotype profiles may include information generated by applying one or more rules to a genomic profile, or information about genotype correlations that are applied to a genomic profile. Phenotype profiles may be generated by applying rules that correlate a plurality of genotypes with a phenotype. The probability or estimate may be expressed as a numerical value, such as a percentage, a numerical risk factor or a numerical confidence interval. The probability may also be expressed as high, moderate, or low. The phenotype profiles may also indicate the presence or absence of a phenotype or the risk of developing a phenotype. For example, a phenotype profile may indicate the presence of blue eyes, or a high risk of developing diabetes. The phenotype profiles may also indicate a predicted prognosis, effectiveness of a treatment, or response to a treatment of a medical condition.

The term risk profile refers to a collection of GCI scores for more than one disease or condition. GCI scores are based on analysis of the association between an individual's genotype with one or more diseases or conditions. Risk profiles may display GCI scores grouped into categories of disease. Further the Risk profiles may display information on how the GCI scores are predicted to change as the individual ages or various risk factors are adjusted. For example, the GCI scores for particular diseases may take into account the effect of changes in diet or preventative measures taken (smoking cessation, drug intake, double radical mastectomies, hysterectomies). The GCI scores may be displayed as a numerical measure, a graphical display, auditory feedback or any combination of the preceding.

As used herein, the term "on-line portal" refers to a source of information which can be readily accessed by an individual through use of a computer and internet website, telephone, or other means that allow similar access to information. The on-line portal may be a secure website. The website may provide links to other secure and non-secure websites, for example links to a secure website with the individual's phenotype profile, or to non-secure websites such as a message board for individuals sharing a specific phenotype.

The practice of the present invention may employ, unless otherwise indicated, conventional techniques and descriptions of molecular biology, cell biology, biochemistry, and immunology, which are within the skill of the art. Such conventional techniques include nucleic acid isolation, polymer array synthesis, hybridization, ligation, and detection of hybridization using a label. Specific illustrations of suitable techniques are exemplified and referenced herein. However, other equivalent conventional procedures can also be used. Other conventional techniques and descriptions can be found in standard laboratory manuals and texts such as Genome Analysis: A Laboratory Manual Series (Vols. I-IV), PCR Primer: A Laboratory Manual, Molecular Cloning: A Laboratory Manual (all from Cold Spring Harbor Laboratory Press); Stryer, L. (1995) Biochemistry (4th Ed.) Freeman, New York; Gait, "Oligonucleotide Synthesis: A Practical Approach" 1984, IRL Press, London, Nelson and Cox (2000); Lehninger, Principles of Biochemistry 3rd Ed., W.H. Freeman Pub., New York, N.Y.; and Berg et al. (2002) Biochemistry, 5th Ed., W.H. Freeman Pub., New York, N.Y., all of which are herein incorporated in their entirety by reference for all purposes.

The methods of the present invention involve analysis of an individual's genomic profile to provide the individual with molecular information relating to a phenotype. As detailed herein, the individual provides a genetic sample, from which a personal genomic profile is generated. The data of the individual's genomic profile is queried for genotype correlations by comparing the profile against a database of established and validated human genotype correlations. The database of established and validated genotype correlations may be from peer-reviewed literature and further judged by a committee of one or more experts in the field, such as geneticists, epidemiologists, or statisticians, and curated. In preferred embodiments, rules are made based on curated genotype correlations and are applied to an individual's genomic profile to generate a phenotype profile. Results of the analysis of the individual's genomic profile, phenotype profile, along with interpretation and supportive information, are provided to the individual of the individual's health care manager, to empower personalized choices for the individual's health care.

A method of the invention is detailed as in FIG. **1**, where an individual's genomic profile is first generated. An individual's genomic profile will contain information about an individual's genes based on genetic variations or markers. Genetic variations are genotypes, which make up genomic profiles. Such genetic variations or markers include, but are not limited to, single nucleotide polymorphisms, single and/or multiple nucleotide repeats, single and/or multiple nucleotide deletions, microsatellite repeats (small numbers of nucleotide repeats with a typical 5-1,000 repeat units), di-nucleotide repeats, tri-nucleotide repeats, sequence rearrangements (including translocation and duplication), copy number variations (both loss and gains at specific loci), and the like. Other genetic variations include chromosomal duplications and translocations as well as centromeric and telomeric repeats.

Genotypes may also include haplotypes and diplotypes. In some embodiments, genomic profiles may have at least 100,000, 300,000, 500,000, or 1,000,000 genotypes. In some embodiments, the genomic profile may be substantially the complete genomic sequence of an individual. In other embodiments, the genomic profile is at least 60%, 80%, or 95% of the complete genomic sequence of an individual. The genomic profile may be approximately 100% of the complete genomic sequence of an individual. Genetic samples that contain the targets include, but are not limited to, unamplified genomic DNA or RNA samples or amplified DNA (or cDNA). The targets may be particular regions of genomic DNA that contain genetic markers of particular interest.

In step **102** of FIG. **1**, a genetic sample of an individual is isolated from a biological sample of an individual. Such biological samples include, but are not limited to, blood, hair, skin, saliva, semen, urine, fecal material, sweat, buccal, and various bodily tissues. In some embodiments, tissues samples may be directly collected by the individual, for example, a buccal sample may be obtained by the individual taking a swab against the inside of their cheek. Other samples such as saliva, semen, urine, fecal material, or sweat, may also be supplied by the individual themselves. Other biological samples may be taken by a health care specialist, such as a phlebotomist, nurse or physician. For example, blood samples may be withdrawn from an individual by a nurse. Tissue biopsies may be performed by a health care specialist, and kits are also available to health care specialists to efficiently obtain samples. A small cylinder of skin may be removed or a needle may be used to remove a small sample of tissue or fluids.

In some embodiments, kits are provided to individuals with sample collection containers for the individual's biological sample. The kit may also provide instructions for an individual to directly collect their own sample, such as how much hair, urine, sweat, or saliva to provide. The kit may also contain instructions for an individual to request tissue samples to be taken by a health care specialist. The kit may include locations where samples may be taken by a third party, for example kits may be provided to health care facilities who in turn collect samples from individuals. The kit may also provide return packaging for the sample to be sent to a sample processing facility, where genetic material is isolated from the biological sample in step **104**.

A genetic sample of DNA or RNA may be isolated from a biological sample according to any of several well-known biochemical and molecular biological methods, see, e.g., Sambrook, et al., Molecular Cloning: A Laboratory Manual (Cold Spring Harbor Laboratory, New York) (1989). There are also several commercially available kits and reagents for isolating DNA or RNA from biological samples, such as those available from DNA Genotek, Gentra Systems, Qiagen, Ambion, and other suppliers. Buccal sample kits are readily available commercially, such as the MasterAmp™ Buccal Swab DNA extraction kit from Epicentre Biotechnologies, as are kits for DNA extraction from blood samples such as Extract-N-Amp™ from Sigma Aldrich. DNA from other tissues may be obtained by digesting the tissue with proteases and heat, centrifuging the sample, and using phenol-chloroform to extract the unwanted materials, leaving the DNA in the aqueous phase. The DNA can then be further isolated by ethanol precipitation.

In a preferred embodiment, genomic DNA is isolated from saliva. For example, using DNA self collection kit technology available from DNA Genotek, an individual collects a specimen of saliva for clinical processing. The sample conveniently can be stored and shipped at room temperature. After delivery of the sample to an appropriate laboratory for processing, DNA is isolated by heat denaturing and protease digesting the sample, typically using reagents supplied by the collection kit supplier at 50° C. for at least one hour. The sample is next centrifuged, and the supernatant is ethanol precipitated. The DNA pellet is suspended in a buffer appropriate for subsequent analysis.

In another embodiment, RNA may be used as the genetic sample. In particular, genetic variations that are expressed can be identified from mRNA. The term "messenger RNA" or "mRNA" includes, but is not limited to pre-mRNA transcript(s), transcript processing intermediates, mature mRNA(s) ready for translation and transcripts of the gene or genes, or nucleic acids derived from the mRNA transcript(s). Transcript processing may include splicing, editing and degradation. As used herein, a nucleic acid derived from an mRNA transcript refers to a nucleic acid for whose synthesis the mRNA transcript or a subsequence thereof has ultimately served as a template. Thus, a cDNA reverse transcribed from an mRNA, a DNA amplified from the cDNA, an RNA transcribed from the amplified DNA, etc., are all derived from the mRNA transcript. RNA can be isolated from any of several bodily tissues using methods known in the art, such as isolation of RNA from unfractionated whole blood using the PAXgene™ Blood RNA System available from PreAnalytiX. Typically, mRNA will be used to reverse transcribe cDNA, which will then be used or amplified for gene variation analysis.

Prior to genomic profile analysis, a genetic sample will typically be amplified, either from DNA or cDNA reverse transcribed from RNA. DNA can be amplified by a number of methods, many of which employ PCR. See, for example, PCR Technology: Principles and Applications for DNA Amplification (Ed. H. A. Erlich, Freeman Press, NY, N.Y., 1992); PCR Protocols: A Guide to Methods and Applications (Eds. Innis, et al., Academic Press, San Diego, Calif., 1990); Mattila et al., Nucleic Acids Res. 19, 4967 (1991); Eckert et al., PCR Methods and Applications 1, 17 (1991); PCR (Eds. McPherson et al., IRL Press, Oxford); and U.S. Pat. Nos. 4,683,202, 4,683,195, 4,800,159 4,965,188, and 5,333,675, and each of which is incorporated herein by reference in their entireties for all purposes.

Other suitable amplification methods include the ligase chain reaction (LCR) (for example, Wu and Wallace, Genomics 4, 560 (1989), Landegren et al., Science 241, 1077 (1988) and Barringer et al. Gene 89:117 (1990)), transcription amplification (Kwoh et al., *Proc. Natl. Acad. Sci. USA* 86:1173-1177 (1989) and WO88/10315), self-sustained sequence replication (Guatelli et al., *Proc. Nat. Acad. Sci. USA,* 87:1874-1878 (1990) and WO90/06995), selective amplification of target polynucleotide sequences (U.S. Pat. No. 6,410,276), consensus sequence primed polymerase chain reaction (CP-PCR) (U.S. Pat. No. 4,437,975), arbitrarily primed polymerase chain reaction (AP-PCR) (U.S. Pat. Nos. 5,413,909, 5,861,245) nucleic acid based sequence amplification (NABSA), rolling circle amplification (RCA), multiple displacement amplification (MDA) (U.S. Pat. Nos. 6,124,120 and 6,323,009) and circle-to-circle amplification (C2CA) (Dahl et al. *Proc. Natl. Acad. Sci* 101:4548-4553 (2004)). (See, U.S. Pat. Nos. 5,409,818, 5,554,517, and 6,063,603, each of which is incorporated herein by reference). Other amplification methods that may be used are described in, U.S. Pat. Nos. 5,242,794, 5,494,810, 5,409,818, 4,988,617, 6,063,603 and 5,554,517 and in U.S. Ser. No. 09/854,317, each of which is incorporated herein by reference.

Generation of a genomic profile in step **106** is performed using any of several methods. Several methods are known in the art to identify genetic variations and include, but are not limited to, DNA sequencing by any of several methodologies, PCR based methods, fragment length polymorphism assays (restriction fragment length polymorphism (RFLP), cleavage fragment length polymorphism (CFLP)) hybridization methods using an allele-specific oligonucleotide as a template (e.g., TaqMan PCR method, the invader method, the DNA chip method), methods using a primer extension reaction, mass spectrometry (MALDI-TOF/MS method), and the like.

In one embodiment, a high density DNA array is used for SNP identification and profile generation. Such arrays are commercially available from Affymetrix and Illumina (see Affymetrix GeneChip® 500K Assay Manual, Affymetrix, Santa Clara, Calif. (incorporated by reference); Sentrix® humanHap650Y genotyping beadchip, Illumina, San Diego, Calif.).

For example, a SNP profile can be generated by genotyping more than 900,000 SNPs using the Affymetrix Genome Wide Human SNP Array 6.0. Alternatively, more than 500,000 SNPs through whole-genome sampling analysis may be determined by using the Affymetrix GeneChip Human Mapping 500K Array Set. In these assays, a subset of the human genome is amplified through a single primer amplification reaction using restriction enzyme digested, adaptor-ligated human genomic DNA. As shown in FIG. **2**, the concentration of the ligated DNA may then be determined. The amplified DNA is then fragmented and the quality of the sample determined prior to continuing with step **106**. If the samples meet the PCR and fragmentation standards, the sample is denatured, labeled, and then hybridized to a microarray consisting of small DNA probes at specific locations on a coated quartz surface. The amount of label that hybridizes to each probe as a function of the amplified DNA sequence is monitored, thereby yielding sequence information and resultant SNP genotyping.

Use of the Affymetrix GeneChip 500K Assay is carried out according to the manufacturer's directions. Briefly, isolated genomic DNA is first digested with either a NspI or StyI restriction endonuclease. The digested DNA is then ligated with a NspI or StyI adaptor oligonucleotide that respectively anneals to either the NspI or StyI restricted DNA. The adaptor-containing DNA following ligation is then amplified by PCR to yield amplified DNA fragments between about 200 and 1100 base pairs, as confirmed by gel electrophoresis. PCR products that meet the amplification standard are purified and quantified for fragmentation. The PCR products are fragmented with DNase I for optimal DNA chip hybridization. Following fragmentation, DNA fragments should be less than 250 base pairs, and on average, about 180 base pairs, as confirmed by gel electrophoresis. Samples that meet the fragmentation standard are then labeled with a biotin compound using terminal deoxynucleotidyl transferase. The labeled fragments are next denatured and then hybridized into a GeneChip 250K array. Following hybridization, the array is stained prior to scanning in a three step process consisting of a streptavidin phycoerythin (SAPE) stain, followed by an antibody amplification step with a biotinylated, anti-streptavidin antibody (goat), and final stain with streptavidin phycoerythin (SAPE). After labeling, the array is covered with an array holding buffer and then scanned with a scanner such as the Affymetrix GeneChip Scanner 3000.

Analysis of data following scanning of an Affymetrix GeneChip Human Mapping 500K Array Set is performed according to the manufacturer's guidelines, as shown in FIG. **3**. Briefly, acquisition of raw data using GeneChip Operating Software (GCOS) occurs. Data may also be aquired using Affymetrix GeneChip Command Console™. The aquisition of raw data is followed by analysis with GeneChip Genotyping Analysis Software (GTYPE). For purposes of the present invention, samples with a GTYPE call rate of less than 80% are excluded. Samples are then examined with BRLMM and/or SNiPer algorithm analyses. Samples with a BRLMM call rate of less than 95% or a SNiPer call rate of less than 98% are excluded. Finally, an association analysis is performed, and samples with a SNiPer quality index of less than 0.45 and/or a Hardy-Weinberg p-value of less than 0.00001 are excluded.

As an alternative to or in addition to DNA microarray analysis, genetic variations such as SNPs and mutations can be detected by DNA sequencing. DNA sequencing may also be used to sequence a substantial portion, or the entire, genomic sequence of an individual. Traditionally, common DNA sequencing has been based on polyacrylamide gel fractionation to resolve a population of chain-terminated fragments (Sanger et al., *Proc. Natl. Acad. Sci. USA* 74:5463-5467 (1977)). Alternative methods have been and continue to be developed to increase the speed and ease of DNA sequencing. For example, high throughput and single molecule sequencing platforms are commercially available or under development from 454 Life Sciences (Branford, Conn.) (Margulies et al., *Nature* (2005) 437:376-380 (2005)); Solexa (Hayward, Calif.); Helicos BioSciences Corporation (Cambridge, Mass.) (U.S. application Ser. No. 11/167,046, filed Jun. 23, 2005), and Li-Cor Biosciences (Lincoln, Nebr.) (U.S. application Ser. No. 11/118031, filed Apr. 29, 2005).

After an individual's genomic profile is generated in step **106**, the profile is stored digitally in step **108**, such profile may be stored digitally in a secure manner. The genomic profile is encoded in a computer readable format to be stored as part of a data set and may be stored as a database, where the genomic profile may be "banked", and can be accessed again later. The data set comprises a plurality of data points, wherein each data point relates to an individual. Each data point may have a plurality of data elements. One data element is the unique identifier, used to identify the individual's genomic profile. It may be a bar code. Another data element is genotype information, such as the SNPs or nucleotide sequence of the individual's genome. Data elements corresponding to the genotype information may also be included in the data point. For example, if the genotype information includes SNPs identified by microarray analysis, other data elements may include the microarray SNP identification number, the SNP rs number, and the polymorphic nucleotide. Other data elements may be chromosome position of the genotype information, quality metrics of the data, raw data files, images of the data, and extracted intensity scores.

The individual's specific factors such as physical data, medical data, ethnicity, ancestry, geography, gender, age, family history, known phenotypes, demographic data, exposure data, lifestyle data, behavior data, and other known phenotypes may also be incorporated as data elements. For example, factors may include, but are not limited to, individual's: birthplace, parents and/or grandparents, relatives' ancestry, location of residence, ancestors' location of residence, environmental conditions, known health conditions, known drug interactions, family health conditions, lifestyle conditions, diet, exercise habits, marital status, and physical measurements, such as weight, height, cholesterol level, heart rate, blood pressure, glucose level and other measurements known in the art The above mentioned factors for an individual's relatives or ancestors, such as parents and grandparents, may also be incorporated as data elements and used to determine an individual's risk for a phenotype or condition.

The specific factors may be obtained from a questionnaire or from a health care manager of the individual. Information from the "banked" profile can then be accessed and utilized as desired. For example, in the initial assessment of an individual's genotype correlations, the individual's entire information (typically SNPs or other genomic sequences across, or taken from an entire genome) will be analyzed for genotype correlations. In subsequent analyses, either the entire information can be accessed, or a portion thereof, from the stored, or banked genomic profile, as desired or appropriate.

Comparison of Genomic Profile with Database of Genotype Correlations.

In step **110**, genotype correlations are obtained from scientific literature. Genotype correlations for genetic variations are determined from analysis of a population of individuals who have been tested for the presence or absence of one or more phenotypic traits of interest and for genotype profile. The alleles of each genetic variation or polymorphism in the profile are then reviewed to determine whether the presence or absence of a particular allele is associated with a trait of interest. Correlation can be performed by standard statistical methods and statistically significant correlations between genetic variations and phenotypic characteristics are noted. For example, it may be determined that the presence of allele A1 at polymorphism A correlates with heart disease. As a further example, it might be found that the combined presence of allele A1 at polymorphism A and allele B1 at polymorphism B correlates with increased risk of cancer. The results of the analyses may be published in peer-reviewed literature, validated by other research groups, and/or analyzed by a committee of experts, such as geneticists, statisticians, epidemiologists, and physicians, and may also be curated.

In FIGS. **4**, **5**, and **6** are examples of correlations between genotypes and phenotypes from which rules to be applied to genomic profiles may be based. For example, in FIGS. **4**A and B, each row corresponds to a phenotype/locus/ethnicity, wherein FIGS. **4**C through I contains further information about the correlations for each of these rows. As an example, in FIG. **4**A, the "Short Phenotype Name" of BC, as noted in FIG. **4**M, an index for the names of the short phenotypes, is an abbreviation for breast cancer. In row BC_4, which is the generic name for the locus, the gene LSP1 is correlated to breast cancer. The published or functional SNP identified with this correlation is rs3817198, as shown in FIG. **4**C, with the published risk allele being C, the nonrisk allele being T. The published SNP and alleles are identified through publications such as seminal publications as in FIGS. **4**E-G. In the example of LSP1 in FIG. **4**E, the seminal publication is Easton et al., Nature 447:713-720 (2007). FIGS. **22** and **25** further list correlations. The correlations in FIGS. **22** and **25** may be used to calculate an individual's risk for a condition or phenotype, for example, for calculating a GCI or GCI Plus score. The GCI or GCI Plus score may also incorporate information such as a condition's prevalence, for example in FIG. **23**.

Alternatively, the correlations may be generated from the stored genomic profiles. For example, individuals with stored genomic profiles may also have known phenotype information stored as well. Analysis of the stored genomic profiles and known phenotypes may generate a genotype correlation. As an example, 250 individuals with stored genomic profiles also have stored information that they have previously been diagnosed with diabetes. Analysis of their genomic profiles is performed and compared to a control group of individuals without diabetes. It is then determined that the individuals previously diagnosed with diabetes have a higher rate of having a particular genetic variant compared to the control group, and a genotype correlation may be made between that particular genetic variant and diabetes.

In step **112**, rules are made based on the validated correlations of genetic variants to particular phenotypes. Rules may be generated based on the genotypes and phenotypes correlated as listed in Table 1, for example. Rules based on correlations may incorporate other factors such as gender (e.g. FIG. **4**) or ethnicity (FIGS. **4** and **5**), to generate effects estimates, such as those in FIGS. **4** and **5**. Other measures resulting from rules may be estimated relative risk increase such as in FIG. **6**. The effects estimates and estimated relative risk increase may be from the published literature, or calculated from the published literature. Alternatively, the rules may be based on correlations generated from stored genomic profiles and previously known phenotypes. In some embodiments, the rules are based on correlations in FIGS. **22** and **25**.

In a preferred embodiment, the genetic variants will be SNPs. While SNPs occur at a single site, individuals who carry a particular SNP allele at one site often predictably carry specific SNP alleles at other sites. A correlation of SNPs and an allele predisposing an individual to disease or condition occurs through linkage disequilibrium, in which the non-random association of alleles at two or more loci occur more or less frequently in a population than would be expected from random formation through recombination.

Other genetic markers or variants, such as nucleotide repeats or insertions, may also be in linkage disequilibrium with genetic markers that have been shown to be associated with specific phenotypes. For example, a nucleotide insertion is correlated with a phenotype and a SNP is in linkage disequilibrium with the nucleotide insertion. A rule is made based on the correlation between the SNP and the phenotype. A rule based on the correlation between the nucleotide insertion and the phenotype may also be made. Either rules or both rules may be applied to a genomic profile, as the presence of one SNP may give a certain risk factor, the other may give another risk factor, and when combined may increase the risk.

Through linkage disequilibrium, a disease predisposing allele cosegregates with a particular allele of a SNP or a combination of particular alleles of SNPs. A particular combination of SNP alleles along a chromosome is termed a haplotype, and the DNA region in which they occur in combination can be referred to as a haplotype block. While a haplotype block can consist of one SNP, typically a haplotype block represents a contiguous series of 2 or more SNPs exhibiting low haplotype diversity across individuals and with generally low recombination frequencies. An identification of a haplotype can be made by identification of one or more SNPs that lie in a haplotype block. Thus, a SNP profile typically can be used to identify haplotype blocks without necessarily requiring identification of all SNPs in a given haplotype block.

Genotype correlations between SNP haplotype patterns and diseases, conditions or physical states are increasingly becoming known. For a given disease, the haplotype patterns of a group of people known to have the disease are compared to a group of people without the disease. By analyzing many individuals, frequencies of polymorphisms in a population can be determined, and in turn these frequencies or genotypes can be associated with a particular phenotype, such as a disease or a condition. Examples of known SNP-disease correlations include polymorphisms in Complement Factor H in age-related macular degeneration (Klein et al., *Science:* 308: 385-389, (2005)) and a variant near the INSIG2 gene associated with obesity (Herbert et al., *Science:* 312:279-283 (2006)). Other known SNP correlations include polymorphisms in the 9p21 region that includes CDKN2A and B, such as) such as rs10757274, rs2383206, rs13333040, rs2383207, and rs10116277 correlated to myocardial infarction (Helgadottir et al., *Science* 316:1491-1493 (2007); McPherson et al., *Science* 316:1488-1491 (2007))

The SNPs may be functional or non-functional. For example, a functional SNP has an effect on a cellular function, thereby resulting in a phenotype, whereas a non-functional SNP is silent in function, but may be in linkage disequilibrium with a functional SNP. The SNPs may also be synonymous or non-synonymous. SNPs that are synonymous are SNPs in which the different forms lead to the same polypeptide sequence, and are non-functional SNPs. If the SNPs lead to different polypeptides, the SNP is non-synonymous and may or may not be functional. SNPs, or other genetic markers, used to identify haplotypes in a diplotype, which is 2 or more haplotypes, may also be used to correlate phenotypes associated with a diplotype. Information about an individual's haplotypes, diplotypes, and SNP profiles may be in the genomic profile of the individual.

In preferred embodiments, for a rule to be generated based on a genetic marker in linkage disequilibrium with another genetic marker that is correlated with a phenotype, the genetic marker may have a r^2 or D' score, scores commonly used in the art to determine linkage disequilibrium, of greater than 0.5. In preferred embodiments, the score is greater than 0.6, 0.7, 0.8, 0.90, 0.95 or 0.99. As a result, in the present invention, the genetic marker used to correlate a phenotype to an individual's genomic profile may be the same as the functional or published SNP correlated to a phenotype, or different. For example, using BC_4, the test SNP and published SNP are the same, as are the test risk and nonrisk alleles are the same as the published risk and nonrisk alleles (FIGS. **4**A and C). However, for BC_5, CASP8 and its correlation to breast cancer, the test SNP is different from its functional or published SNP, as are the test risk and nonrisk alleles to the published risk and nonrisk alleles. The test and published alleles are oriented relative to the plus strand of the genome, and from these columns, it can be inferred the homozygous risk or nonrisk genotype, which may generate a rule to be applied to the genomic profile of individuals such as subscribers. In some embodiments, the test SNP may not yet be identified, but using the published SNP information, allelic differences or SNPs may be identified based on another assay, such as TaqMan. For example, AMD_5 in FIG. **25**A, the published SNP is rs1061170 but a test SNP has not been identified. The test SNP may be identified by LD analysis with the published SNP. Alternatively, the test SNP may not be used, and instead, TaqMan or other comparable assay, will be used to assess an individual's genome having the test SNP.

The test SNPs may be "DIRECT" or "TAG" SNPs (FIGS. **4**E-G, FIG. **5**). Direct SNPs are the test SNPs that are the same as the published or functional SNP, such as for BC_4. Direct SNPs may also be used for FGFR2 correlation with breast cancer, using the SNP rs1073640 in Europeans and Asians, where the minor allele is A and the other allele is G (Easton et al., *Nature* 447:1087-1093 (2007)). Another published or functional SNP for FGFR2 correlation to breast cancer is rs1219648, also in Europeans and Asians (Hunter et al., *Nat. Genet.* 39:870-874 (2007)). Tag SNPs are where the test SNP is different from that of the functional or published SNP, as in for BC_5. Tag SNPs may also be used for other genetic variants such as SNPs for CAMTA1 (rs4908449), 9p21 (rs10757274, rs2383206, rs13333040, rs2383207, rs10116277), COL1A1 (rs1800012), FVL (rs6025), HLA-DQA1 (rs4988889, rs2588331), eNOS (rs1799983), MTHFR (rs1801133), and APC (rs28933380).

Databases of SNPs are publicly available from, for example, the International HapMap Project (see www.hapmap.org, *The International HapMap Consortium, Nature* 426:789-796 (2003), and *The International HapMap Consortium, Nature* 437:1299-1320 (2005)), the Human Gene Mutation Database (HGMD) public database (see www.hgmd.org), and the Single Nucleotide Polymorphism database (dbSNP) (see www.ncbi.nlm.nih.gov/SNP/). These databases provide SNP haplotypes, or enable the determination of SNP haplotype patterns. Accordingly, these SNP databases enable examination of the genetic risk factors underlying a wide range of diseases and conditions, such as cancer, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, and infectious diseases. The diseases or conditions may be actionable, in which treatments and therapies currently exist. Treatments may include prophylactic treatments as well as treatments that ameliorate symptoms and conditions, including lifestyle changes.

Many other phenotypes such as physical traits, physiological traits, mental traits, emotional traits, ethnicity, ancestry, and age may also be examined. Physical traits may include height, hair color, eye color, body, or traits such as stamina, endurance, and agility. Mental traits may include intelligence, memory performance, or learning performance. Ethnicity and ancestry may include identification of ancestors or ethnicity, or where an individual's ancestors originated from. The age may be a determination of an individual's real age, or the age in which an individual's genetics places them in relation to the general population. For example, an individual's real age is 38 years of age, however their genetics may determine their memory capacity or physical well-being may be of the average 28 year old. Another age trait may be a projected longevity for an individual.

Other phenotypes may also include non-medical conditions, such as "fun" phenotypes. These phenotypes may include comparisons to well known individuals, such as foreign dignitaries, politicians, celebrities, inventors, athletes, musicians, artists, business people, and infamous individuals, such as convicts. Other "fun" phenotypes may include comparisons to other organisms, such as bacteria, insects, plants, or non-human animals. For example, an individual may be interested to see how their genomic profile compares to that of their pet dog, or to a former president.

At step **114**, the rules are applied to the stored genomic profile to generate a phenotype profile of step **116**. For example, information in FIG. **4**, **5**, or **6** may form the basis of rules, or tests, to apply to an individual's genomic profile. The rules may encompass the information on test SNP and alleles, and the effect estimates of FIG. **4**, where the UNITS for effect estimate is the units of the effect estimate, such as OR, or odds-ratio (95% confidence interval) or mean. The effects estimate may be a genotypic risk (FIGS. **4**C-G) in preferred embodiments, such as the risk for homozygotes (homoz or RR), risk heterozygotes (heteroz or RN), and nonrisk homozygotes (homoz or NN). In other embodiments, the effect estimate may be carrier risk, which is RR or RN vs NN. In yet other embodiments, the effect estimate may be based on the allele, an allelic risk such as R vs. N. There may also be two locus (FIG. **4**J) or three locus (FIG. **4**K) genotypic effect estimate (e.g. RRRR, RRNN, etc for the 9 possible genotype combinations for a two locus effect estimate). The test SNP frequency in the public HapMap is also noted in FIGS. **4**H and I.

In other embodiments, information from FIGS. **21**, **22**, **23**, and/or **25** may be used to generate information to apply to an individual's genomic profile. For example, the information may be used to generate GCI or GCI Plus scores for an individual (for example, FIG. **19**). The scores may be used to generate information on genetic risks, such as estimated lifetime risk, for one or more conditions in the phenotype profile of an individual (for example, FIG. **15**). the methods allow calculating estimated lifetime risks or relative risks for one or more phenotypes or conditions as listed in FIG. **22** or **25**. The risk for a single condition may be based on one or more SNP. For example, an estimated risk for a phenotype or condition may be based on at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 SNPs, wherein the SNPs for estimating a risk may be published SNPs, test SNPs, or both (for example, FIG. **25**).

The estimated risk for a condition may be based on the SNPs as listed in FIG. **22** or **25**. In some embodiments, the risk for a condition may be based on at least one SNP. For example, assessment of an individual's risk for Alzheimers (AD), colorectal cancer (CRC), osteoarthritis (OA) or exfoliation glaucoma (XFG), may be based on 1 SNP (for example, rs4420638 for AD, rs6983267 for CRC, rs4911178 for OA and rs2165241 for XFG). For other conditions, such as obesity (BMIOB), Graves' disease (GD), or hemochromatosis (HEM), an individual's estimated risk may be based on at least 1 or 2 SNPs (for example, rs9939609 and/or rs9291171 for BMIOB; DRB1*0301 DQA1*0501 and/or rs3087243 for GD; rs1800562 and/or rs129128 for HEM). For conditions such as, but not limited to, myocardial infarction (MI), multiple sclerosis (MS), or psoriasis (PS), 1, 2, or 3 SNPs may be used to assess an individual's risk for the condition (for example, rs1866389, rs1333049, and/or rs6922269 for MI; rs6897932, rs12722489, and/or DRB1*1501 for MS; rs6859018, rs11209026, and/or HLAC*0602 for PS). For estimating an individual's risk of restless legs syndrome (RLS) or celiac disease (CelD), 1, 2, 3, or 4 SNPs (for example, rs6904723, rs2300478, rs1026732, and/or rs9296249 for RLS; rs6840978, rs11571315, rs2187668, and/or DQA1*0301 DQB1*0302 for CelD). For prostate cancer (PC) or lupus (SLE), 1, 2, 3, 4, or 5 SNPs may be used to estimate an individual's risk for PC or SLE (for example, rs4242384, rs6983267, rs16901979, rs17765344, and/or rs4430796 for PC; rs12531711, rs10954213, rs2004640, DRB1*0301, and/or DRB1*1501 for SLE). For estimating an individual's lifetime risk of macular degeneration (AMD) or rheumatoid arthritis (RA), 1, 2, 3, 4, 5, or 6 SNPs, may be used (for example, rs10737680, rs10490924, rs541862, rs2230199, rs1061170, and/or rs9332739 for AMD; rs6679677, rs11203367, rs6457617, DRB*0101, DRB1*0401, and/or DRB1*0404 for RA). For estimating an individual's lifetime risk of breast cancer (BC), 1, 2, 3, 4, 5, 6 or 7 SNPs may be used (for example, rs3803662, rs2981582, rs4700485, rs3817198, rs17468277, rs6721996, and/or rs3803662). For estimating an individual's lifetime risk of Crohn's disease (CD) or Type 2 diabetes (T2D), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 SNPs may be used (for example, rs2066845, rs5743293, rs10883365, rs17234657, rs10210302, rs9858542, rs11805303, rs1000113, rs17221417, rs2542151, and/or rs10761659 for CD; rs13266634, rs4506565, rs10012946, rs7756992, rs10811661, rs12288738, rs8050136, rs1111875, rs4402960, rs5215, and/or rs1801282 for T2D). In some embodiments, the SNPs used as a basis for determining risk may be in linkage disequilibrium with the SNPs as mentioned above, or listed in FIG. **22** or **25**.

The phenotype profile of an individual may comprise a number of phenotypes. In particular, the assessment of a patient's risk of disease or other conditions such as likely drug response including metabolism, efficacy and/or safety, by the methods of the present invention allows for prognostic or diagnostic analysis of susceptibility to multiple, unrelated diseases and conditions, whether in symptomatic, presymptomatic or asymptomatic individuals, including carriers of one or more disease/condition predisposing alleles. Accordingly, these methods provide for general assessment of an individual's susceptibility to disease or condition without any preconceived notion of testing for a specific disease or condition. For example, the methods of the present invention allow for assessment of an individual's susceptibility to any of the several conditions listed in Tables 1, FIG. **4**, **5**, or **6**, based on the individual's genomic profile. Furthermore, the methods allow assessments of an individual's estimated lifetime risk or relative risk for one or more phenotype or condition, such as those in FIG. **22** or **25**.

The assessment preferably provides information for 2 or more of these conditions, and more preferably, 3, 4, 5, 10, 20, 50, 100 or even more of these conditions. In preferred embodiments, the phenotype profile results from the application of at least 20 rules to the genomic profile of an individual. In other embodiments, at least 50 rules are applied to the genomic profile of an individual. A single rule for a phenotype may be applied for monogenic phenotypes. More than one rule may also be applied for a single phenotype, such as a multigenic phenotype or a monogenic phenotype wherein multiple genetic variants within a single gene affects the probability of having the phenotype.

Following an initial screening of an individual patient's genomic profile, updates of an individual's genotype correlations are made (or are available) through comparisons to additional nucleotide variants, such as SNPs, when such additional nucleotide variants become known. For example, step **110** may be performed periodically, for example, daily, weekly, or monthly by one or more people of ordinary skill in the field of genetics, who scan scientific literature for new genotype correlations. The new genotype correlations may then be further validated by a committee of one or more experts in the field. Step **112** may then also be periodically updated with new rules based on the new validated correlations.

The new rule may encompass a genotype or phenotype without an existing rule. For example, a genotype not correlated with any phenotype is discovered to correlate with a new or existing phenotype. A new rule may also be for a correlation between a phenotype for which no genotype has previously been correlated to. New rules may also be determined for genotypes and phenotypes that have existing rules. For example, a rule based on the correlation between genotype A and phenotype A exists. New research reveals genotype B correlates with phenotype A, and a new rule based on this correlation is made. Another example is phenotype B is discovered to be associated with genotype A, and thus a new rule may be made.

Rules may also be made on discoveries based on known correlations but not initially identified in published scientific literature. For example, it may be reported genotype C is correlated with phenotype C. Another publication reports genotype D is correlated with phenotype D. Phenotype C and D are related symptoms, for example phenotype C may be shortness of breath, and phenotype D is small lung capacity. A correlation between genotype C and phenotype D, or genotype D with phenotype C, may be discovered and validated through statistical means with existing stored genomic profiles of individuals with genotypes C and D, and phenotypes C and D, or by further research. A new rule may then be generated based on the newly discovered and validated correlation. In another embodiment, stored genomic profiles of a number of individuals with a specific or related phenotype may be studied to determine a genotype common to the individuals, and a correlation may be determined. A new rule may be generated based on this correlation.

Rules may also be made to modify existing rules. For example, correlations between genotypes and phenotypes may be partly determined by a known individual characteristic, such as ethnicity, ancestry, geography, gender, age, family history, or any other known phenotypes of the individual. Rules based on these known individual characteristics may be made and incorporated into an existing rule, to provide a modified rule. The choice of modified rule to be applied will be dependent on the specific individual factor of an individual. For example, a rule may be based on the probability an individual who has phenotype E is 35% when the individual has genotype E. However, if an individual is of a particular ethnicity, the probability is 5%. A new rule may be generated based on this result and applied to individuals with that particular ethnicity. Alternatively, the existing rule with a determination of 35% may be applied, and then another rule based on ethnicity for that phenotype is applied. The rules based on known individual characteristics may be determined from scientific literature or determined based on studies of stored genomic profiles. New rules may be added and applied to genomic profiles in step **114**, as the new rules are developed, or they may be applied periodically, such as at least once a year.

Information of an individual's risk of disease can also be expanded as technology advances allow for finer resolution SNP genomic profiles. As indicated above, an initial SNP genomic profile readily can be generated using microarray technology for scanning of 500,000 SNPs. Given the nature of haplotype blocks, this number allows for a representative profile of all SNPs in an individual's genome. Nonetheless, there are approximately 10 million SNPs estimated to occur commonly in the human genome (the International HapMap Project; www.hapmap.org). As technological advances allow for practical, cost-efficient resolution of SNPs at a finer level of detail, such as microarrays of 1,000,000, 1,500,000, 2,000,000, 3,000,000, or more SNPs, or whole genomic sequencing, more detailed SNP genomic profiles can be generated. Likewise, cost-efficient analysis of finer SNP genomic profiles and updates to the master database of SNP-disease correlations will be enabled by advances in computational analytical methodology.

After generation of phenotype profile at step **116**, a subscriber or their health care manager may access their genomic or phenotype profiles via an on-line portal or website as in step **118**. Reports containing phenotype profiles and other information related to the phenotype and genomic profiles may also be provided to the subscriber or their health care manager, as in steps **120** and **122**. The reports may be printed, saved on the subscriber's computer, or viewed on-line.

A sample on-line report is shown in FIG. **7**. The subscriber may choose to display a single phenotype, or more than one phenotype. The subscriber may also have different viewing options, for example, as shown in FIG. **7**, a "Quick View" option. The phenotype may be a medical condition and different treatments and symptoms in the quick report may link to other web pages that contain further information about the treatment. For example, by clicking on a drug, it will lead to website that contains information about dosages, costs, side effects, and effectiveness. It may also compare the drug to other treatments. The website may also contain a link leading to the drug manufacturer's website. Another link may provide an option for the subscriber to have a pharmacogenomic profile generated, which would include information such as their likely response to the drug based on their genomic profile. Links to alternatives to the drug may also be provided, such as preventative action such as fitness and weight loss, and links to diet supplements, diet plans, and to nearby health clubs, health clinics, health and wellness providers, day spas and the like may also be provided. Educational and informational videos, summaries of available treatments, possible remedies, and general recommendations may also be provided.

The on-line report may also provide links to schedule in-person physician or genetic counseling appointments or to access an on-line genetic counselor or physician, providing the opportunity for a subscriber to ask for more information regarding their phenotype profile. Links to on-line genetic counseling and physician questions may also be provided on the on-line report.

Reports may also be viewed in other formats such as a comprehensive view for a single phenotype, wherein more detail for each category is provided. For example, there may be more detailed statistics about the likelihood of the subscriber developing the phenotype, more information about the typical symptoms or phenotypes, such as sample symptoms for a medical condition, or the range of a physical non-medical condition such as height, or more information about the gene and genetic variant, such as the population incidence, for example in the world, or in different countries, or in different age ranges or genders. For example, FIG. **15** shows a summary of estimated lifetime risks for a number of conditions. The individual may view more information for a specific condition, such as prostate cancer (FIG. **16**) or Crohn's disease (FIG. **17**).

In another embodiment, the report may be of a "fun" phenotype, such as the similarity of an individual's genomic profile to that of a famous individual, such as Albert Einstein. The report may display a percentage similarity between the individual's genomic profile to that of Einstein's, and may further display a predicted IQ of Einstein and that of the individual's. Further information may include how the genomic profile of the general population and their IQ compares to that of the individual's and Einstein's.

In another embodiment, the report may display all phenotypes that have been correlated to the subscriber's genomic profile. In other embodiments, the report may display only the phenotypes that are positively correlated with an individual's genomic profile. In other formats, the individual may choose to display certain subgroups of phenotypes, such as only medical phenotypes, or only actionable medical phenotypes. For example, actionable phenotypes and their correlated genotypes, may include Crohn's disease (correlated with IL23R and CARD 15), Type 1 diabetes (correlated with HLA-DR/DQ), lupus (correlated HLA-DRB1), psoriasis (HLA-C), multiple sclerosis (HLA-DQA1), Graves disease (HLA-DRB1), rheumatoid arthritis (HLA-DRB1), Type 2 diabetes (TCF7L2), breast cancer (BRCA2), colon cancer (APC), episodic memory (KIBRA), and osteoporosis (COL1A1). The individual may also choose to display subcategories of phenotypes in their report, such as only inflammatory diseases for medical conditions, or only physical traits for non-medical conditions. In some embodiments, the individual may choose to show all conditions an estimated risk was calculated for the individual by highlighting those conditions (for example, FIG. **15**A, D), highlighting only conditions with an elevated risk (FIG. **15**B), or only conditions with a reduced risk (FIG. **15**C).

Information submitted by and conveyed to an individual may be secure and confidential, and access to such information may be controlled by the individual. Information derived from the complex genomic profile may be supplied to the individual as regulatory agency approved, understandable, medically relevant and/or high impact data. Information may also be of general interest, and not medically relevant. Information can be securely conveyed to the individual by several means including, but not restricted to, a portal interface and/or mailing. More preferably, information is securely (if so elected by the individual) provided to the individual by a portal interface, to which the individual has secure and confidential access. Such an interface is preferably provided by on-line, internet website access, or in the alternative, telephone or other means that allow private, secure, and readily available access. The genomic profiles, phenotype profiles, and reports are provided to an individual or their health care manager by transmission of the data over a network.

Accordingly, FIG. **8** is a block diagram showing a representative example logic device through which a phenotype profile and report may be generated. FIG. **8** shows a computer system (or digital device) **800** to receive and store genomic profiles, analyze genotype correlations, generate rules based on the analysis of genotype correlations, apply the rules to the genomic profiles, and produce a phenotype profile and report. The computer system **800** may be understood as a logical apparatus that can read instructions from media **811** and/or network port **805**, which can optionally be connected to server **809** having fixed media **812**. The system shown in FIG. **8** includes CPU **801**, disk drives **803**, optional input devices such as keyboard **815** and/or mouse **816** and optional monitor **807**. Data communication can be achieved through the indicated communication medium to a server **809** at a local or a remote location. The communication medium can include any means of transmitting and/or receiving data. For example, the communication medium can be a network connection, a wireless connection or an internet connection. Such a connection can provide for communication over the World Wide Web. It is envisioned that data relating to the present invention can be transmitted over such networks or connections for reception and/or review by a party **822**. The receiving party **822** can be but is not limited to an individual, a subscriber, a health care provider or a health care manager. In one embodiment, a computer-readable medium includes a medium suitable for transmission of a result of an analysis of a biological sample or a genotype correlation. The medium can include a result regarding a phenotype profile of an individual subject, wherein such a result is derived using the methods described herein.

A personal portal will preferably serve as the primary interface with an individual for receiving and evaluating genomic data. A portal will enable individuals to track the progress of their sample from collection through testing and results. Through portal access, individuals are introduced to relative risks for common genetic disorders based on their genomic profile. The subscriber may choose which rules to apply to their genomic profile through the portal.

In one embodiment, one or more web pages will have a list of phenotypes and next to each phenotype a box in which a subscriber may select to include in their phenotype profile. The phenotypes may be linked to information on the phenotype, to help the subscriber make an informed choice about the phenotype they want included in their phenotype profile. The webpage may also have phenotypes organized by disease groups, for example as actionable diseases or not. For example, a subscriber may choose actionable phenotypes only, such as HLA-DQA1 and celiac disease. The subscriber may also choose to display pre or post symptomatic treatments for the phenotypes. For example, the individual may choose actionable phenotypes with pre-symptomatic treatments (outside of increased screening), for celiac disease, a pre-symptomatic treatment of gluten free diet. Another example may be Alzheimer's, the pre-symptomatic treatment of statins, exercise, vitamins, and mental activity. Thrombosis is another example, with a pre-symptomatic treatment of avoid oral contraceptives and avoid sitting still for long periods of time. An example of a phenotype with an approved post symptomatic treatment is wet AMD, correlated with CFH, wherein individuals may obtain laser treatment for their condition.

The phenotypes may also be organized by type or class of disease or conditions, for example neurological, cardiovascular, endocrine, immunological, and so forth. Phenotypes may also be grouped as medical and non-medical phenotypes. Other groupings of phenotypes on the webpage may be by physical traits, physiological traits, mental traits, or emotional traits. The webpage may further provide a section in which a group of phenotypes are chosen by selection of one box. For example, a selection for all phenotypes, only medically relevant phenotypes, only non-medically relevant phenotypes, only actionable phenotypes, only non-actionable phenotypes, different disease group, or "fun" phenotypes. "Fun" phenotypes may include comparisons to celebrities or other famous individuals, or to other animals or even other organisms. A list of genomic profiles available for comparison may also be provided on the webpage for selection by the subscriber to compare to the subscriber's genomic profile.

The on-line portal may also provide a search engine, to help the subscriber navigate the portal, search for a specific phenotype, or search for specific terms or information revealed by their phenotype profile or report. Links to access partner services and product offerings may also be provided by the portal. Additional links to support groups, message boards, and chat rooms for individuals with a common or similar phenotype may also be provided. The on-line portal may also provide links to other sites with more information on the phenotypes in a subscriber's phenotype profile. The on-line portal may also provide a service to allow subscribers to share their phenotype profile and reports with friends, families, or health care managers. Subscribers may choose which phenotypes to show in the phenotype profile they want shared with their friends, families, or health care managers.

The phenotype profiles and reports provide a personalized genotype correlation to an individual. The genotype correlations provided to an individual can be used in determining personal health care and lifestyle choices. If a strong correlation is found between a genetic variant and a disease for which treatment is available, detection of the genetic variant may assist in deciding to begin treatment of the disease and/or monitoring of the individual. In the case where a statistically significant correlation exists but is not regarded as a strong correlation, an individual can review the information with a personal physician and decide an appropriate, beneficial course of action. Potential courses of action that could be beneficial to an individual in view of a particular genotype correlation include administration of therapeutic treatment, monitoring for potential need of treatment or effects of treatment, or making life-style changes in diet, exercise, and other personal habits/activities. For example, an actionable phenotype such as celiac disease may have a pre-symptomatic treatment of a gluten-free diet. Likewise, genotype correlation information could be applied through pharmacogenomics to predict the likely response an individual would have to treatment with a particular drug or regimen of drugs, such as the likely efficacy or safety of a particular drug treatment.

Subscribers may choose to provide the genomic and phenotype profiles to their health care managers, such as a physician or genetic counselor. The genomic and phenotype profiles may be directly accessed by the healthcare manager, by the subscriber printing out a copy to be given to the healthcare manager, or have it directly sent to the healthcare manager through the on-line portal, such as through a link on the on-line report.

Delivery of this pertinent information will empower patients to act in concert with their physician. In particular, discussions between patients and their physicians can be empowered through an individual's portal and links to medical information, and the ability to tie patient's genomic information into their medical records. Medical information may include prevention and wellness information. The information provided to the individual patient by the present invention will enable patients to make informed choices for their health care. In this manner, patients will be able to make choices that may help them avoid and/or delay diseases that their individual genomic profile (inherited DNA) makes more likely. In addition, patients will be able to employ a treatment regime that personally fits their specific medical needs. Individuals also will have the ability to access their genotype data should they develop an illness and need this information to help their physician form a therapeutic strategy.

Genotype correlation information could also be used in cooperation with genetic counseling to advise couples considering reproduction, and potential genetic concerns to the mother, father and/or child. Genetic counselors may provide information and support to subscribers with phenotype profiles that display an increased risk for specific conditions or diseases. They may interpret information about the disorder, analyze inheritance patterns and risks of recurrence, and review available options with the subscriber. Genetic counselors may also provide supportive counseling refer subscribers to community or state support services. Genetic counseling may be included with specific subscription plans. In some embodiments, genetic counseling may be scheduled within 24 hours of request and available during of hours such as evenings, Saturdays, Sundays, and/or holidays.

An individual's portal will also facilitate delivery of additional information beyond an initial screening. Individuals will be informed about new scientific discoveries that relate to their personal genetic profile, such as information on new treatments or prevention strategies for their current or potential conditions. The new discoveries may also be delivered to their healthcare managers. In preferred embodiments, the subscribers, or their healthcare providers are informed of new genotype correlations and new research about the phenotypes in the subscriber's phenotype profiles, by e-mail. In other embodiments, e-mails of "fun" phenotypes are sent to subscribers, for example, an e-mail may inform them that their genomic profile is 77% identical to that of Abraham Lincoln and that further information is available via an on-line portal.

The present invention also provides a system of computer code for generating new rules, modifying rules, combining rules, periodically updating the rule set with new rules, maintaining a database of genomic profile securely, applying the rules to the genomic profiles to determine phenotype profiles, and for generating reports. Computer code for notifying subscribers of new or revised correlations new or revised rules, and new or revised reports, for example with new prevention and wellness information, information about new therapies in development, or new treatments available.

Business Method

The present invention provides a business method of assessing an individual's genotype correlations based on comparison of the patient's genome profile against a clinically-derived database of established, medically relevant nucleotide variants. The present invention further provides a business method for using the stored genomic profile of the individual for assessing new correlations that were not initially known, to generate updated phenotype profiles for an individual, without the requirement of the individual submitting another biological sample. A flow chart illustrating the business method is in FIG. **9**.

A revenue stream for the subject business method is generated in part at step **101**, when an individual initially requests and purchases a personalized genomic profile for genotype correlations for a multitude of common human diseases, conditions, and physical states. A request and purchase can be made through any number of sources, including but not limited to, an on-line web portal, an on-line health service, and an individual's personal physician or similar source of personal medical attention. In an alternative embodiment, the genomic profile may be provided free, and the revenue stream is generated at a later step, such as step **103**.

A subscriber, or customer, makes a request for purchase of a phenotype profile. In response to a request and purchase, a customer is provided a collection kit for a biological sample used for genetic sample isolation at step **103**. When a request is made on-line, by telephone, or other source in which a collection kit is not readily physically available to the customer, a collection kit is provided by expedited delivery, such as courier service that provides same-day or overnight delivery. Included in the collection kit is a container for a sample, as well as packaging materials for expedited delivery of the sample to a laboratory for genomic profile generation. The kit may also include instructions for sending the sample to the sample processing facility, or laboratory, and instructions for accessing their genomic profile and phenotype profile, which may occur through an on-line portal.

As detailed above, genomic DNA can be obtained from any of a number of types of biological samples. Preferably, genomic DNA is isolated from saliva, using a commercially available collection kit such as that available from DNA Genotek. Use of saliva and such a kit allows for a non-invasive sample collection, as the customer conveniently provides a saliva sample in a container from a collection kit and then seals the container. In addition, a saliva sample can be stored and shipped at room temperature.

After depositing a biological sample into a collection or specimen container, a customer will deliver the sample to a laboratory for processing at step **105**. Typically, the customer may use packaging materials provided in the collection kit to deliver/send the sample to a laboratory by expedited delivery, such as same-day or overnight courier service.

The laboratory that processes the sample and generates the genomic profile may adhere to appropriate governmental agency guidelines and requirements. For example, in the United States, a processing laboratory may be regulated by one or more federal agencies such as the Food and Drug Administration (FDA) or the Centers for Medicare and Medicaid Services (CMS), and/or one or more state agencies. In the United States, a clinical laboratory may be accredited or approved under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

At step **107**, the laboratory processes the sample as previously described to isolate the genetic sample of DNA or RNA. Analysis of the isolated genetic sample and generation of a genomic profile is then performed at step **109**. Preferably, a genomic SNP profile is generated. As described above, several methodologies may be used to generate a SNP profile. Preferably, a high density array, such as the commercially available platforms from Affymetrix or Illumina, is used for SNP identification and profile generation. For example, a SNP profile may be generated using an Affymetrix GeneChip assay, as described above in more detail. As technology evolves, there may be other technology vendors who can generate high density SNP profiles. In another embodiment, a genomic profile for a subscriber will be the genomic sequence of the subscriber.

Following generation of an individual's genomic profile, the genotype data is preferably encrypted, imported at step **111**, and deposited into a secure database or vault at step **113**, where the information is stored for future reference. The genomic profile and related information may be confidential, with access to this proprietary information and the genomic profile limited as directed by the individual and/or his or her personal physician. Others, such as family and the genetic counselor of the individual may also be permitted access by the subscriber.

The database or vault may be located on-site with the processing laboratory. Alternatively, the database may be located at a separate location. In this scenario, the genomic profile data generated by the processing lab can be imported at step **111** to a separate facility that contains the database.

After an individual's genomic profile is generated, the individual's genetic variations are then compared against a clinically-derived database of established, medically relevant genetic variants in step **115**. Alternatively, the genotype correlations may not be medically relevant but still incorporated into the database of genotype correlations, for example, physical traits such as eye color, or "fun" phenotypes such as genomic profile similarity to a celebrity.

The medically relevant SNPs may have been established through the scientific literature and related sources. The non-SNP genetic variants may also be established to be correlated with phenotypes. Generally, the correlation of SNPs to a given disease is established by comparing the haplotype patterns of a group of people known to have the disease to a group of people without the disease. By analyzing many individuals, frequencies of polymorphisms in a population can be determined, and in turn these genotype frequencies can be associated with a particular phenotype, such as a disease or a condition. Alternatively, the phenotype may be a non-medical condition.

The relevant SNPs and non-SNP genetic variants may also be determined through analysis of the stored genomic profiles of individuals rather than determined by available published literature. Individuals with stored genomic profiles may disclose phenotypes that have previously been determined. Analysis of the genotypes and disclosed phenotypes of the individuals may be compared to those without the phenotypes to determine a correlation that may then be applied to other genomic profiles. Individuals that have their genomic profiles determined may fill out questionnaires about phenotypes that have previously been determined. Questionnaires may contain questions about medical and non-medical conditions, such as diseases previously diagnosed, family history of medical conditions, lifestyle, physical traits, mental traits, age, social life, environment and the like.

In one embodiment, an individual may have their genomic profile determined free of charge if they fill out a questionnaire. In some embodiments, the questionnaires are to be filled out periodically by the individuals in order to have free access to their phenotype profile and reports. In other embodiments, the individuals that fill out the questionnaires may be entitled to a subscription upgrade, such that they have more access than their previous subscription level, or they may purchase or renew a subscription at a reduced cost.

All information deposited in the database of medically relevant genetic variants at step **121** is first approved by a research/clinical advisory board for scientific accuracy and importance, coupled with review and oversight by an appropriate governmental agency if warranted at step **119**. For example, in the United States, the FDA may provide oversight through approval of algorithms used for validation of genetic variant (typically SNP, transcript level, or mutation) correlative data. At step **123**, scientific literature and other relevant sources are monitored for additional genetic variant-disease or condition correlations, and following validation of their accuracy and importance, along with governmental agency review and approval, these additional genotype correlations are added to the master database at step **125**.

The database of approved, validated medically-relevant genetic variants, coupled with a genome-wide individual profile, will advantageously allow genetic risk-assessment to be performed for a large number of diseases or conditions. Following compilation of an individual's genomic profile, individual genotype correlations can be determined through comparison of the individual's nucleotide (genetic) variants or markers with a database of human nucleotide variants that have been correlated to a particular phenotype, such as a disease, condition, or physical state. Through comparison of an individual's genomic profile to the master database of genotype correlations, the individual can be informed whether they are found to be positive or negative for a genetic risk factor, and to what degree. An individual will receive relative risk and/or predisposition data on a wide range of scientifically validated disease states (e.g., Alzheimer's, cardiovascular disease, blood clotting). For example, genotype correlations in Table 1 may be included. In addition, SNP disease correlations in the database may include, but are not limited to, those correlations shown in FIG. **4**. Other correlations from FIGS. **5** and **6** may also be included. The subject business method therefore provides analysis of risk to a multitude of diseases and conditions without any preconceived notion of what those diseases and conditions might entail.

In other embodiments, the genotype correlations that are coupled to the genome wide individual profile are non-medically relevant phenotypes, such as "fun" phenotypes or physical traits such as hair color. In preferred embodiments, a rule or rule set is applied to the genomic profile or SNP profile of an individual, as described above. Application of the rules to a genomic profile generates a phenotype profile for the individual.

Accordingly, the master database of human genotype correlations is expanded with additional genotype correlations as new correlations become discovered and validated. An update can be made by accessing pertinent information from the individual's genomic profile stored in a database as desired or appropriate. For example, a new genotype correlation that becomes known may be based on a particular gene variant. Determination of whether an individual may be susceptible to that new genotype correlation can then be made by retrieving and comparing just that gene portion of the individual's entire genomic profile.

The results of the genomic query preferably are analyzed and interpreted so as to be presented to the individual in an understandable format. At step **117**, the results of an initial screening are then provided to the patient in a secure, confidential form, either by mailing or through an on-line portal interface, as detailed above.

The report may contain the phenotype profile as well as genomic information about the phenotypes in the phenotype profile, for example basic genetics about the genes involved or the statistics of the genetic variants in different populations. Other information based on the phenotype profile that may be included in the report are prevention strategies, wellness information, therapies, symptom awareness, early detection schemes, intervention schemes, and refined identification and sub-classification of the phenotypes. Following an initial screening of an individual's genomic profile, controlled, moderated updates are or can be made.

Updates of an individual's genomic profile are made or are available in conjunction with updates to the master database as new genotype correlations emerge and are both validated and approved. New rules based on the new genotype correlations may be applied to the initial genomic profile to provide updated phenotype profiles. An updated genotype correlation profile can be generated by comparing the relevant portion of the individual's genomic profile to a new genotype correlation at step **127**. For example, if a new genotype correlation is found based on variation in a particular gene, then that gene portion of the individual's genomic profile can be analyzed for the new genotype correlation. In such a case, one or more new rules may be applied to generate an updated phenotype profile, rather than an entire rule set with rules that had already been applied. The results of the individual's updated genotype correlations are provided in a secure manner at step **129**.

Initial and updated phenotype profiles may be a service provided to subscribers or customers. Varying levels of subscriptions to genomic profile analysis and combinations thereof can be provided. Likewise, subscription levels can vary to provide individuals choices of the amount of service they wish to receive with their genotype correlations. Thus, the level of service provided would vary with the level of service subscription purchased by the individual.

An entry level subscription for a subscriber may include a genomic profile and an initial phenotype profile. This may be a basic subscription level. Within the basic subscription level may be varying levels of service. For example, a particular subscription level could provide references for genetic counseling, physicians with particular expertise in treating or preventing a particular disease, and other service options. Genetic counseling may be obtained on-line or by telephone. In another embodiment, the price of the subscription may depend on the number of phenotypes an individual chooses for their phenotype profile. Another option may be whether the subscriber chooses to access on-line genetic counseling.

In another scenario, a subscription could provide for an initial genome-wide, genotype correlation, with maintenance of the individual's genomic profile in a database; such database may be secure if so elected by the individual. Following this initial analysis, subsequent analyses and additional results could be made upon request and additional payment by the individual. This may be a premium level of subscription.

In one embodiment of the subject business method, updates of an individual's risks are performed and corresponding information made available to individuals on a subscription basis. The updates may be available to subscribers who purchase the premium level of subscription. Subscription to genotype correlation analysis can provide updates with a particular category or subset of new genotype correlations according to an individual's preferences. For example, an individual might only wish to learn of genotype correlations for which there is a known course of treatment or prevention. To aid an individual in deciding whether to have an additional analysis performed, the individual can be provided with information regarding additional genotype correlations that have become available. Such information can be conveniently mailed or e-mailed to a subscriber.

Within the premium subscription, there may be further levels of service, such as those mentioned in the basic subscription. Other subscription models may be provided within the premium level. For example, the highest level may provide a subscriber to unlimited updates and reports. The subscriber's profile may be updated as new correlations and rules are determined. At this level, subscribers may also permit access to unlimited number of individuals, such as family members and health care managers. The subscribers may also have unlimited access to on-line genetic counselors and physicians.

The next level of subscription within the premium level may provide more limited aspects, for example a limited number of updates. The subscriber may have a limited number of updates for their genomic profile within a subscription period, for example, 4 times a year. In another subscription level, the subscriber may have their stored genomic profile updated once a week, once a month, or once a year. In another embodiment, the subscriber may only have a limited number of phenotypes they may choose to update their genomic profile against.

A personal portal will also conveniently allow an individual to maintain a subscription to risk or correlation updates and information updates or alternatively, make requests for updated risk assessment and information. As described above, varying subscription levels could be provided to allow individuals choices of various levels of genotype correlation results and updates and may different subscription levels may be chosen by the subscriber via their personal portal.

Any of these subscription options will contribute to the revenue stream for the subject business method. The revenue stream for the subject business method will also be added by the addition of new customers and subscribers, wherein the new genomic profiles are added to the database.

TABLE 1

Representative genes having genetic variants correlated with a phenotype.

Gene	Phenotype
A2M	Alzheimer's Disease
ABCA1	cholesterol, HDL
ABCB1	HIV
ABCB1	epilepsy
ABCB1	kidney transplant complications
ABCB1	digoxin, serum concentration
ABCB1	Crohn's disease; ulcerative colitis
ABCB1	Parkinson's disease
ABCC8	Type 2 diabetes
ABCC8	diabetes, type 2
ABO	myocardial infarct
ACADM	medium-chain acyl-CoA dehydrogenase deficiency
ACDC	Type 2, diabetes
ACE	Type 2 diabetes
ACE	hypertension
ACE	Alzheimer's Disease
ACE	myocardial infarction
ACE	cardiovascular
ACE	left ventricular hypertrophy
ACE	coronary artery disease
ACE	atherosclerosis, coronary
ACE	retinopathy, diabetic
ACE	systemic lupus erythematosus
ACE	blood pressure, arterial
ACE	erectile dysfunction
ACE	Lupus
ACE	polycystic kidney disease
ACE	stroke
ACP1	diabetes, type 1
ACSM1 (LIP)c	cholesterol levels
ADAM33	asthma
ADD1	hypertension
ADD1	blood pressure, arterial
ADH1B	alcohol abuse
ADH1C	alcohol abuse
ADIPOQ	diabetes, type 2
ADIPOQ	obesity
ADORA2A	panic disorder
ADRB1	hypertension
ADRB1	heart failure
ADRB2	asthma
ADRB2	hypertension
ADRB2	obesity
ADRB2	blood pressure, arterial
ADRB2	Type 2 Diabetes
ADRB3	obesity
ADRB3	Type 2 Diabetes
ADRB3	hypertension
AGT	hypertension
AGT	Type 2 diabetes
AGT	Essential Hypertension
AGT	myocardial infarction
AGTR1	hypertension
AGTR2	hypertension

TABLE 1-continued

Representative genes having genetic variants correlated with a phenotype.

Gene	Phenotype
AHR	breast cancer
ALAD	lead toxicity
ALDH2	alcoholism
ALDH2	alcohol abuse
ALDH2	colorectal cancer
ALDRL2	Type 2 diabetes
ALOX5	asthma
ALOX5AP	asthma
APBB1	Alzheimer's Disease
APC	colorectal cancer
APEX1	lung cancer
APOA1	atherosclerosis, coronary
APOA1	cholesterol, HDL
APOA1	coronary artery disease
APOA1	Type 2 diabetes
APOA4	Type 2 diabetes
APOA5	triglycerides
APOA5	atherosclerosis, coronary
APOB	hypercholesterolemia
APOB	obesity
APOB	cardiovascular
APOB	coronary artery disease
APOB	coronary heart disease
APOB	Type 2 diabetes
APOC1	Alzheimer's Disease
APOC3	triglycerides
APOC3	Type 2 Diabetes
APOE	Alzheimer's Disease
APOE	Type 2 diabetes
APOE	multiple sclerosis
APOE	atherosclerosis, coronary
APOE	Parkinson's disease
APOE	coronary heart disease
APOE	myocardial infarction
APOE	stroke
APOE	Alzheimer's disease
APOE	coronary artery disease
APP	Alzheimer's Disease
AR	prostate cancer
AR	breast cancer
ATM	breast cancer
ATP7B	Wilson disease
ATXN8OS	spinocerebellar ataxia
BACE1	Alzheimer's Disease
BCHE	Alzheimer's Disease
BDKRB2	hypertension
BDNF	Alzheimer's Disease
BDNF	bipolar disorder
BDNF	Parkinson's disease
BDNF	schizophrenia
BDNF	memory
BGLAP	bone density
BRAF	thyroid cancer
BRCA1	breast cancer
BRCA1	breast cancer; ovarian cancer
BRCA1	ovarian cancer
BRCA2	breast cancer
BRCA2	breast cancer; ovarian cancer
BRCA2	ovarian cancer
BRIP1	breast cancer
C4A	systemic lupus erythematosus
CALCR	bone density
CAMTA1	episodic memory
CAPN10	diabetes, type 2
CAPN10	Type 2 diabetes
CAPN3	muscular dystrophy
CARD15	Crohn's disease
CARD15	Crohn's disease; ulcerative colitis
CARD15	Inflammatory Bowel Disease
CART	obesity
CASR	bone density
CCKAR	schizophrenia
CCL2	systemic lupus erythematosus
CCL5	HIV
CCL5	asthma

TABLE 1-continued

Representative genes having genetic variants correlated with a phenotype.

Gene	Phenotype
CCND1	colorectal cancer
CCR2	HIV
CCR2	HIV infection
CCR2	hepatitis C
CCR2	myocardial infarct
CCR3	Asthma
CCR5	HIV
CCR5	HIV infection
CCR5	hepatitis C
CCR5	asthma
CCR5	multiple sclerosis
CD14	atopy
CD14	asthma
CD14	Crohn's disease
CD14	Crohn's disease; ulcerative colitis
CD14	periodontitis
CD14	Total IgE
CDH1	prostate cancer
CDH1	colorectal cancer
CDKN2A	melanoma
CDSN	psoriasis
CEBPA	leukemia, myeloid
CETP	atherosclerosis, coronary
CETP	coronary heart disease
CETP	hypercholesterolemia
CFH	macular degeneration
CFTR	cystic fibrosis
CFTR	pancreatitis
CFTR	Cystic Fibrosis
CHAT	Alzheimer's Disease
CHEK2	breast cancer
CHRNA7	schizophrenia
CMA1	atopic dermatitis
CNR1	schizophrenia
COL1A1	bone density
COL1A1	osteoporosis
COL1A2	bone density
COL2A1	Osteoarthritis
COMT	schizophrenia
COMT	breast cancer
COMT	Parkinson's disease
COMT	bipolar disorder
COMT	obsessive compulsive disorder
COMT	alcoholism
CR1	systemic lupus erythematosus
CRP	C-reactive protein
CST3	Alzheimer's Disease
CTLA4	Type 1 diabetes
CTLA4	Graves' disease
CTLA4	multiple sclerosis
CTLA4	rheumatoid arthritis
CTLA4	systemic lupus erythematosus
CTLA4	lupus erythematosus
CTLA4	celiac disease
CTSD	Alzheimer's Disease
CX3CR1	HIV
CXCL12	HIV
CXCL12	HIV infection
CYBA	atherosclerosis, coronary
CYBA	hypertension
CYP11B2	hypertension
CYP11B2	left ventricular hypertrophy
CYP17A1	breast cancer
CYP17A1	prostate cancer
CYP17A1	endometriosis
CYP17A1	endometrial cancer
CYP19A1	breast cancer
CYP19A1	prostate cancer
CYP19A1	endometriosis
CYP1A1	lung cancer
CYP1A1	breast cancer
CYP1A1	Colorectal Cancer
CYP1A1	prostate cancer
CYP1A1	esophageal cancer
CYP1A1	endometriosis

TABLE 1-continued

Representative genes having genetic variants correlated with a phenotype.

Gene	Phenotype
CYP1A1	cytogenetic studies
CYP1A2	schizophrenia
CYP1A2	colorectal cancer
CYP1B1	breast cancer
CYP1B1	glaucoma
CYP1B1	prostate cancer
CYP21A2	21-hydroxylase deficiency
CYP21A2	congenital adrenal hyperplasia
CYP21A2	adrenal hyperplasia, congenital
CYP2A6	smoking behavior
CYP2A6	nicotine
CYP2A6	lung cancer
CYP2C19	H. pylori infection
CYP2C19	phenytoin
CYP2C19	gastric disease
CYP2C8	malaria, plasmodium falciparum
CYP2C9	anticoagulant complications
CYP2C9	warfarin sensitivity
CYP2C9	warfarin therapy, response to
CYP2C9	colorectal cancer
CYP2C9	phenytoin
CYP2C9	acenocoumarol response
CYP2C9	coagulation disorder
CYP2C9	hypertension
CYP2D6	colorectal cancer
CYP2D6	Parkinson's disease
CYP2D6	CYP2D6 poor metabolizer phenotype
CYP2E1	lung cancer
CYP2E1	colorectal cancer
CYP3A4	prostate cancer
CYP3A5	prostate cancer
CYP3A5	esophageal cancer
CYP46A1	Alzheimer's Disease
DBH	schizophrenia
DHCR7	Smith-Lemli-Opitz syndrome
DISC1	schizophrenia
DLST	Alzheimer's Disease
DMD	muscular dystrophy
DRD2	alcoholism
DRD2	schizophrenia
DRD2	smoking behavior
DRD2	Parkinson's disease
DRD2	tardive dyskinesia
DRD3	schizophrenia
DRD3	tardive dyskinesia
DRD3	bipolar disorder
DRD4	attention deficit hyperactivity disorder
DRD4	schizophrenia
DRD4	novelty seeking
DRD4	ADHD
DRD4	personality traits
DRD4	heroin abuse
DRD4	alcohol abuse
DRD4	alcoholism
DRD4	personality disorders
DTNBP1	schizophrenia
EDN1	hypertension
EGFR	lung cancer
ELAC2	prostate cancer
ENPP1	Type 2 diabetes
EPHB2	prostate cancer
EPHX1	lung cancer
EPHX1	colorectal cancer
EPHX1	cytogenetic studies
EPHX1	chronic obstructive pulmonary disease/COPD
ERBB2	breast cancer
ERCC1	lung cancer
ERCC1	colorectal cancer
ERCC2	lung cancer
ERCC2	cytogenetic studies
ERCC2	bladder cancer
ERCC2	colorectal cancer
ESR1	bone density
ESR1	bone mineral density
ESR1	breast cancer

TABLE 1-continued

Representative genes having genetic variants correlated with a phenotype.

Gene	Phenotype
ESR1	endometriosis
ESR1	osteoporosis
ESR2	bone density
ESR2	breast cancer
estrogen receptor	bone mineral density
F2	coronary heart disease
F2	stroke
F2	thromboembolism, venous
F2	preeclampsia
F2	thrombosis
F5	thromboembolism, venous
F5	preeclampsia
F5	myocardial infarct
F5	stroke
F5	stroke, ischemic
F7	atherosclerosis, coronary
F7	myocardial infarct
F8	hemophilia
F9	hemophilia
FABP2	Type 2 diabetes
FAS	Alzheimer's Disease
FASLG	multiple sclerosis
FCGR2A	systemic lupus erythematosus
FCGR2A	lupus erythematosus
FCGR2A	periodontitis
FCGR2A	rheumatoid arthritis
FCGR2B	lupus erythematosus
FCGR2B	systemic lupus erythematosus
FCGR3A	systemic lupus erythematosus
FCGR3A	lupus erythematosus
FCGR3A	periodontitis
FCGR3A	arthritis
FCGR3A	rheumatoid arthritis
FCGR3B	periodontitis
FCGR3B	periodontal disease
FCGR3B	lupus erythematosus
FGB	fibrinogen
FGB	myocardial infarction
FGB	coronary heart disease
FLT3	leukemia, myeloid
FLT3	leukemia
FMR1	Fragile X syndrome
FRAXA	Fragile X Syndrome
FUT2	H. pylori infection
FVL	Factor V Leiden
G6PD	G6PD deficiency
G6PD	hyperbilirubinemia
GABRA5	bipolar disorder
GBA	Gaucher disease
GBA	Parkinson's disease
GCGR (FAAH, ML4R, UCP2)	body mass/obesity
GCK	Type 2 diabetes
GCLM (F12, TLR4)	atherosclerosis, myocardial infarction
GDNF	schizophrenia
GHRL	obesity
GJB1	Charcot-Marie-Tooth disease
GJB2	deafness
GJB2	hearing loss, sensorineural nonsyndromic
GJB2	hearing loss, sensorineural
GJB2	hearing loss/deafness
GJB6	hearing loss, sensorineural nonsyndromic
GJB6	hearing loss/deafness
GNAS	hypertension
GNB3	hypertension
GPX1	lung cancer
GRIN1	schizophrenia
GRIN2B	schizophrenia
GSK3B	bipolar disorder
GSTM1	lung cancer
GSTM1	colorectal cancer
GSTM1	breast cancer
GSTM1	prostate cancer
GSTM1	cytogenetic studies
GSTM1	bladder cancer

TABLE 1-continued

Representative genes having genetic variants correlated with a phenotype.

Gene	Phenotype
GSTM1	esophageal cancer
GSTM1	head and neck cancer
GSTM1	leukemia
GSTM1	Parkinson's disease
GSTM1	stomach cancer
GSTP1	Lung cancer
GSTP1	colorectal cancer
GSTP1	breast cancer
GSTP1	cytogenetic studies
GSTP1	prostate cancer
GSTT1	lung cancer
GSTT1	colorectal cancer
GSTT1	breast cancer
GSTT1	prostate cancer
GSTT1	Bladder Cancer
GSTT1	cytogenetic studies
GSTT1	asthma
GSTT1	benzene toxicity
GSTT1	esophageal cancer
GSTT1	head and neck cancer
GYS1	Type 2 diabetes
HBB	thalassemia
HBB	thalassemia, beta
HD	Huntington's disease
HFE	Hemochromatosis
HFE	iron levels
HFE	colorectal cancer
HK2	Type 2 diabetes
HLA	rheumatoid arthritis
HLA	Type 1 diabetes
HLA	Behcet's Disease
HLA	celiac disease
HLA	psoriasis
HLA	Graves disease
HLA	multiple sclerosis
HLA	schizophrenia
HLA	asthma
HLA	diabetes mellitus
HLA	Lupus
HLA-A	leukemia
HLA-A	HIV
HLA-A	diabetes, type 1
HLA-A	graft-versus-host disease
HLA-A	multiple sclerosis
HLA-B	leukemia
HLA-B	Behcet's Disease
HLA-B	celiac disease
HLA-B	diabetes, type 1
HLA-B	graft-versus-host disease
HLA-B	sarcoidosis
HLA-C	psoriasis
HLA-DPA1	measles
HLA-DPB1	diabetes, type 1
HLA-DPB1	Asthma
HLA-DQA1	diabetes, type 1
HLA-DQA1	celiac disease
HLA-DQA1	cervical cancer
HLA-DQA1	asthma
HLA-DQA1	multiple sclerosis
HLA-DQA1	diabetes, type 2; diabetes, type 1
HLA-DQA1	lupus erythematosus
HLA-DQA1	pregnancy loss, recurrent
HLA-DQA1	psoriasis
HLA-DQB1	diabetes, type 1
HLA-DQB1	celiac disease
HLA-DQB1	multiple sclerosis
HLA-DQB1	cervical cancer
HLA-DQB1	lupus erythematosus
HLA-DQB1	pregnancy loss, recurrent
HLA-DQB1	arthritis
HLA-DQB1	asthma
HLA-DQB1	HIV
HLA-DQB1	lymphoma
HLA-DQB1	tuberculosis
HLA-DQB1	rheumatoid arthritis

TABLE 1-continued

Representative genes having genetic variants correlated with a phenotype.

Gene	Phenotype
HLA-DQB1	diabetes, type 2
HLA-DQB1	graft-versus-host disease
HLA-DQB1	narcolepsy
HLA-DQB1	arthritis, rheumatoid
HLA-DQB1	cholangitis, sclerosing
HLA-DQB1	diabetes, type 2; diabetes, type 1
HLA-DQB1	Graves' disease
HLA-DQB1	hepatitis C
HLA-DQB1	hepatitis C, chronic
HLA-DQB1	malaria
HLA-DQB1	malaria, plasmodium falciparum
HLA-DQB1	melanoma
HLA-DQB1	psoriasis
HLA-DQB1	Sjogren's syndrome
HLA-DQB1	systemic lupus erythematosus
HLA-DRB1	diabetes, type 1
HLA-DRB1	multiple sclerosis
HLA-DRB1	systemic lupus erythematosus
HLA-DRB1	rheumatoid arthritis
HLA-DRB1	cervical cancer
HLA-DRB1	arthritis
HLA-DRB1	celiac disease
HLA-DRB1	lupus erythematosus
HLA-DRB1	sarcoidosis
HLA-DRB1	HIV
HLA-DRB1	tuberculosis
HLA-DRB1	Graves' disease
HLA-DRB1	lymphoma
HLA-DRB1	psoriasis
HLA-DRB1	asthma
HLA-DRB1	Crohn's disease
HLA-DRB1	graft-versus-host disease
HLA-DRB1	hepatitis C, chronic
HLA-DRB1	narcolepsy
HLA-DRB1	sclerosis, systemic
HLA-DRB1	Sjogren's syndrome
HLA-DRB1	Type 1 diabetes
HLA-DRB1	arthritis, rheumatoid
HLA-DRB1	cholangitis, sclerosing
HLA-DRB1	diabetes, type 2; diabetes, type 1
HLA-DRB1	H. pylori infection
HLA-DRB1	hepatitis C
HLA-DRB1	juvenile arthritis
HLA-DRB1	leukemia
HLA-DRB1	malaria
HLA-DRB1	melanoma
HLA-DRB1	pregnancy loss, recurrent
HLA-DRB3	psoriasis
HLA-G	pregnancy loss, recurrent
HMOX1	atherosclerosis, coronary
HNF4A	diabetes, type 2
HNF4A	type 2 diabetes
HSD11B2	hypertension
HSD17B1	breast cancer
HTR1A	depressive disorder, major
HTR1B	alcohol dependence
HTR1B	alcoholism
HTR2A	memory
HTR2A	schizophrenia
HTR2A	bipolar disorder
HTR2A	depression
HTR2A	depressive disorder, major
HTR2A	suicide
HTR2A	Alzheimer's Disease
HTR2A	anorexia nervosa
HTR2A	hypertension
HTR2A	obsessive compulsive disorder
HTR2C	schizophrenia
HTR6	Alzheimer's Disease
HTR6	schizophrenia
HTRA1	wet age-related macular degeneration
IAPP	Type 2 Diabetes
IDE	Alzheimer's Disease
IFNG	tuberculosis
IFNG	Type 1 diabetes
IFNG	graft-versus-host disease
IFNG	hepatitis B
IFNG	multiple sclerosis
IFNG	asthma
IFNG	breast cancer
IFNG	kidney transplant
IFNG	kidney transplant complications
IFNG	longevity
IFNG	pregnancy loss, recurrent
IGFBP3	breast cancer
IGFBP3	prostate cancer
IL10	systemic lupus erythematosus
IL10	asthma
IL10	graft-versus-host disease
IL10	HIV
IL10	kidney transplant
IL10	kidney transplant complications
IL10	hepatitis B
IL10	juvenile arthritis
IL10	longevity
IL10	multiple sclerosis
IL10	pregnancy loss, recurrent
IL10	rheumatoid arthritis
IL10	tuberculosis
IL12B	Type 1 diabetes
IL12B	asthma
IL13	asthma
IL13	atopy
IL13	chronic obstructive pulmonary disease/COPD
IL13	Graves' disease
IL1A	periodontitis
IL1A	Alzheimer's Disease
IL1B	periodontitis
IL1B	Alzheimer's Disease
IL1B	stomach cancer
IL1R1	Type 1 diabetes
IL1RN	stomach cancer
IL2	asthma; eczema; allergic disease
IL4	Asthma
IL4	atopy
IL4	HIV
IL4R	asthma
IL4R	atopy
IL4R	Total serum IgE
IL6	Bone Mineralization
IL6	kidney transplant
IL6	kidney transplant complications
IL6	Longevity
IL6	multiple sclerosis
IL6	bone density
IL6	bone mineral density
IL6	Colorectal Cancer
IL6	juvenile arthritis
IL6	rheumatoid arthritis
IL9	asthma
INHA	premature ovarian failure
INS	Type 1 diabetes
INS	Type 2 diabetes
INS	diabetes, type 1
INS	obesity
INS	prostate cancer
INSIG2	obesity
INSR	Type 2 diabetes
INSR	hypertension
INSR	polycystic ovary syndrome
IPF1	diabetes, type 2
IRS1	Type 2 diabetes
IRS1	diabetes, type 2
IRS2	diabetes, type 2
ITGB3	myocardial infarction
ITGB3	atherosclerosis, coronary
ITGB3	coronary heart disease
ITGB3	myocardial infarct
KCNE1	EKG, abnormal
KCNE2	EKG, abnormal

TABLE 1-continued

Representative genes having genetic variants correlated with a phenotype.	
Gene	Phenotype
KCNH2	EKG, abnormal
KCNH2	long QT syndrome
KCNJ11	diabetes, type 2
KCNJ11	Type 2 Diabetes
KCNN3	schizophrenia
KCNQ1	EKG, abnormal
KCNQ1	long QT syndrome
KIBRA	episodic memory
KLK1	hypertension
KLK3	prostate cancer
KRAS	colorectal cancer
LDLR	hypercholesterolemia
LDLR	hypertension
LEP	obesity
LEPR	obesity
LIG4	breast cancer
LIPC	atherosclerosis, coronary
LPL	Coronary Artery Disease
LPL	hyperlipidemia
LPL	triglycerides
LRP1	Alzheimer's Disease
LRP5	bone density
LRRK2	Parkinson's disease
LRRK2	Parkinsons disease
LTA	type 1 diabetes
LTA	Asthma
LTA	systemic lupus erythematosus
LTA	sepsis
LTC4S	Asthma
MAOA	alcoholism
MAOA	schizophrenia
MAOA	bipolar disorder
MAOA	smoking behavior
MAOA	personality disorders
MAOB	Parkinson's disease
MAOB	smoking behavior
MAPT	Parkinson's disease
MAPT	Alzheimer's Disease
MAPT	dementia
MAPT	Frontotemporal dementia
MAPT	progressive supranuclear palsy
MC1R	melanoma
MC3R	obesity
MC4R	obesity
MECP2	Rett syndrome
MEFV	Familial Mediterranean Fever
MEFV	amyloidosis
MICA	Type 1 diabetes
MICA	Behcet's Disease
MICA	celiac disease
MICA	rheumatoid arthritis
MICA	systemic lupus erythematosus
MLH1	colorectal cancer
MME	Alzheimer's Disease
MMP1	Lung Cancer
MMP1	ovarian cancer
MMP1	periodontitis
MMP3	myocardial infarct
MMP3	ovarian cancer
MMP3	rheumatoid arthritis
MPO	lung cancer
MPO	Alzheimer's Disease
MPO	breast cancer
MPZ	Charcot-Marie-Tooth disease
MS4A2	asthma
MS4A2	atopy
MSH2	colorectal cancer
MSH6	colorectal cancer
MSR1	prostate cancer
MTHFR	colorectal cancer
MTHFR	Type 2 diabetes
MTHFR	neural tube defects
MTHFR	homocysteine
MTHFR	thromboembolism, venous
MTHFR	atherosclerosis, coronary

TABLE 1-continued

Representative genes having genetic variants correlated with a phenotype.	
Gene	Phenotype
MTHFR	Alzheimer's Disease
MTHFR	esophageal cancer
MTHFR	preeclampsia
MTHFR	pregnancy loss, recurrent
MTHFR	stroke
MTHFR	thrombosis, deep vein
MT-ND1	diabetes, type 2
MTR	colorectal cancer
MT-RNR1	hearing loss, sensorineural nonsyndromic
MTRR	neural tube defects
MTRR	homocysteine
MT-TL1	diabetes, type 2
MUTYH	colorectal cancer
MYBPC3	cardiomyopathy
MYH7	cardiomyopathy
MYOC	glaucoma, primary open-angle
MYOC	glaucoma
NAT1	colorectal cancer
NAT1	Breast Cancer
NAT1	bladder cancer
NAT2	colorectal cancer
NAT2	bladder cancer
NAT2	breast cancer
NAT2	Lung Cancer
NBN	breast cancer
NCOA3	breast cancer
NCSTN	Alzheimer's Disease
NEUROD1	Type 1 diabetes
NF1	neurofibromatosis1
NOS1	Asthma
NOS2A	multiple sclerosis
NOS3	hypertension
NOS3	coronary heart disease
NOS3	atherosclerosis, coronary
NOS3	coronary artery disease
NOS3	myocardial infarction
NOS3	acute coronary syndrome
NOS3	blood pressure, arterial
NOS3	preeclampsia
NOS3	nitric oxide
NOS3	Alzheimer's Disease
NOS3	asthma
NOS3	Type 2 diabetes
NOS3	cardiovascular disease
NOS3	Behcet's Disease
NOS3	erectile dysfunction
NOS3	kidney failure, chronic
NOS3	lead toxicity
NOS3	left ventricular hypertrophy
NOS3	pregnancy loss, recurrent
NOS3	retinopathy, diabetic
NOS3	stroke
NOTCH4	schizophrenia
NPY	alcohol abuse
NQO1	lung cancer
NQO1	colorectal cancer
NQO1	benzene toxicity
NQO1	bladder cancer
NQO1	Parkinson's Disease
NR3C2	hypertension
NR4A2	Parkinson's disease
NRG1	schizophrenia
NTF3	schizophrenia
OGG1	lung cancer
OGG1	colorectal cancer
OLR1	Alzheimer's Disease
OPA1	glaucoma
OPRM1	alcohol abuse
OPRM1	substance dependence
OPTN	glaucoma, primary open-angle
P450	drug metabolism
PADI4	rheumatoid arthritis
PAH	phenylketonuria/PKU
PAI1	coronary heart disease
PAI1	asthma

TABLE 1-continued

Representative genes having genetic variants correlated with a phenotype.

Gene	Phenotype
PALB2	breast cancer
PARK2	Parkinson's disease
PARK7	Parkinson's disease
PDCD1	lupus erythematosus
PINK1	Parkinson's disease
PKA	memory
PKC	memory
PLA2G4A	schizophrenia
PNOC	schizophrenia
POMC	obesity
PON1	atherosclerosis, coronary
PON1	Parkinson's disease
PON1	Type 2 Diabetes
PON1	atherosclerosis
PON1	coronary artery disease
PON1	coronary heart disease
PON1	Alzheimer's Disease
PON1	longevity
PON2	atherosclerosis, coronary
PON2	preterm delivery
PPARG	Type 2 Diabetes
PPARG	obesity
PPARG	diabetes, type 2
PPARG	Colorectal Cancer
PPARG	hypertension
PPARGC1A	diabetes, type 2
PRKCZ	Type 2 diabetes
PRL	systemic lupus erythematosus
PRNP	Alzheimer's Disease
PRNP	Creutzfeldt-Jakob disease
PRNP	Jakob-Creutzfeldt disease
PRODH	schizophrenia
PRSS1	pancreatitis
PSEN1	Alzheimer's Disease
PSEN2	Alzheimer's Disease
PSMB8	Type 1 diabetes
PSMB9	Type 1 diabetes
PTCH	skin cancer, non-melanoma
PTGIS	hypertension
PTGS2	colorectal cancer
PTH	bone density
PTPN11	Noonan syndrome
PTPN22	rheumatoid arthritis
PTPRC	multiple sclerosis
PVT1	end stage renal disease
RAD51	breast cancer
RAGE	retinopathy, diabetic
RB1	retinoblastoma
RELN	schizophrenia
REN	hypertension
RET	thyroid cancer
RET	Hirschsprung's disease
RFC1	neural tube defects
RGS4	schizophrenia
RHO	retinitis pigmentosa
RNASEL	prostate cancer
RYR1	malignant hyperthermia
SAA1	amyloidosis
SCG2	hypertension
SCG3	obesity
SCGB1A1	asthma
SCN5A	Brugada syndrome
SCN5A	EKG, abnormal
SCN5A	long QT syndrome
SCNN1B	hypertension
SCNN1G	hypertension
SERPINA1	COPD
SERPINA3	Alzheimer's Disease
SERPINA3	COPD
SERPINA3	Parkinson's disease
SERPINE1	myocardial infarct
SERPINE1	Type 2 Diabetes
SERPINE1	atherosclerosis, coronary
SERPINE1	obesity
SERPINE1	preeclampsia

TABLE 1-continued

Representative genes having genetic variants correlated with a phenotype.

Gene	Phenotype
SERPINE1	stroke
SERPINE1	hypertension
SERPINE1	pregnancy loss, recurrent
SERPINE1	thromboembolism, venous
SLC11A1	tuberculosis
SLC22A4	Crohn's disease; ulcerative colitis
SLC22A5	Crohn's disease; ulcerative colitis
SLC2A1	Type 2 diabetes
SLC2A2	Type 2 diabetes
SLC2A4	Type 2 diabetes
SLC3A1	cystinuria
SLC6A3	attention deficit hyperactivity disorder
SLC6A3	Parkinson's disease
SLC6A3	smoking behavior
SLC6A3	alcoholism
SLC6A3	schizophrenia
SLC6A4	depression
SLC6A4	depressive disorder, major
SLC6A4	schizophrenia
SLC6A4	suicide
SLC6A4	alcoholism
SLC6A4	bipolar disorder
SLC6A4	personality traits
SLC6A4	attention deficit hyperactivity disorder
SLC6A4	Alzheimer's Disease
SLC6A4	personality disorders
SLC6A4	panic disorder
SLC6A4	alcohol abuse
SLC6A4	affective disorder
SLC6A4	anxiety disorder
SLC6A4	smoking behavior
SLC6A4	depressive disorder, major; bipolar disorder
SLC6A4	heroin abuse
SLC6A4	irritable bowel syndrome
SLC6A4	migraine
SLC6A4	obsessive compulsive disorder
SLC6A4	suicidal behavior
SLC7A9	cystinuria
SNAP25	ADHD
SNCA	Parkinson's disease
SOD1	ALS/amyotrophic lateral sclerosis
SOD2	breast cancer
SOD2	lung cancer
SOD2	prostate cancer
SPINK1	pancreatitis
SPP1	multiple sclerosis
SRD5A2	prostate cancer
STAT6	asthma
STAT6	Total IgE
SULT1A1	breast cancer
SULT1A1	colorectal cancer
TAP1	Type 1 diabetes
TAP1	lupus erythematosus
TAP2	Type 1 diabetes
TAP2	diabetes, type 1
TBX21	asthma
TBXA2R	asthma
TCF1	diabetes, type 2
TCF1	Type 2 diabetes
TF	Alzheimer's Disease
TGFB1	breast cancer
TGFB1	kidney transplant
TGFB1	kidney transplant complications
TH	schizophrenia
THBD	myocardial infarction
TLR4	asthma
TLR4	Crohn's disease; ulcerative colitis
TLR4	sepsis
TNF	asthma
TNFA	cerebrovascular disease
TNF	Type 1 diabetes
TNF	rheumatoid arthritis
TNF	systemic lupus erythematosus
TNF	kidney transplant
TNF	psoriasis

TABLE 1-continued

Representative genes having genetic variants correlated with a phenotype.

Gene	Phenotype
TNF	sepsis
TNF	Type 2 Diabetes
TNF	Alzheimer's Disease
TNF	Crohn's disease
TNF	diabetes, type 1
TNF	hepatitis B
TNF	kidney transplant complications
TNF	multiple sclerosis
TNF	schizophrenia
TNF	celiac disease
TNF	obesity
TNF	pregnancy loss, recurrent
TNFRSF11B	bone density
TNFRSF1A	rheumatoid arthritis
TNFRSF1B	Rheumatoid Arthritis
TNFRSF1B	systemic lupus erythematosus
TNFRSF1B	arthritis
TNNT2	cardiomyopathy
TP53	lung cancer
TP53	breast cancer
TP53	Colorectal Cancer
TP53	prostate cancer
TP53	cervical cancer
TP53	ovarian cancer
TP53	smoking
TP53	esophageal cancer
TP73	lung cancer
TPH1	suicide
TPH1	depressive disorder, major
TPH1	suicidal behavior
TPH1	schizophrenia
TPMT	thiopurine methyltransferase activity
TPMT	leukemia
TPMT	inflammatory bowel disease
TPMT	thiopurine S-methyltransferase phenotype
TSC1	tuberous sclerosis
TSC2	tuberous sclerosis
TSHR	Graves' disease
TYMS	colorectal cancer
TYMS	stomach cancer
TYMS	esophageal cancer
UCHL1	Parkinson's disease
UCP1	obesity
UCP2	obesity
UCP3	obesity
UGT1A1	hyperbilirubinemia
UGT1A1	Gilbert syndrome
UGT1A6	colorectal cancer
UGT1A7	colorectal cancer
UTS2	diabetes, type 2
VDR	bone density
VDR	prostate cancer
VDR	bone mineral density
VDR	Type 1 diabetes
VDR	osteoporosis
VDR	bone mass
VDR	breast cancer
VDR	lead toxicity
VDR	tuberculosis
VDR	Type 2 diabetes
VEGF	breast cancer
Vit D rec	idiopathic short stature
VKORC1	warfarin therapy, response to
WNK4	hypertension
XPA	lung cancer
XPC	lung cancer
XPC	cytogenetic studies
XRCC1	lung cancer
XRCC1	cytogenetic studies
XRCC1	breast cancer
XRCC1	bladder cancer
XRCC2	breast cancer
XRCC3	breast cancer
XRCC3	cytogenetic studies
XRCC3	lung cancer
XRCC3	bladder cancer
ZDHHC8	schizophrenia

The Genetic Composite Index (GCI)

The etiology of many conditions or diseases is attributed to both genetic and environmental factors. Recent advances in genotyping technology has provided opportunities to identify new associations between diseases and genetic markers across an entire genome. Indeed, many recent studies have discovered such associations, in which a specific allele or genotype is correlated with an increased risk for a disease. Some of these studies involve the collection of a set of test cases and a set of controls, and the comparison of allele distribution of genetic markers between the two populations. In some of these studies the association between a specific genetic markers and a disease is measure in isolation from other genetic markers, which are treated as background and are not accounted for in the statistical analysis.

Genetic markers and variants may include SNPs, nucleotide repeats, nucleotide insertions, nucleotide deletions, chromosomal translocations, chromosomal duplications, or copy number variations. Copy number variation may include microsatellite repeats, nucleotide repeats, centromeric repeats, or telomeric repeats.

In one aspect of the present invention information about the association of multiple genetic markers with one or more diseases or conditions is combined and analyzed to produce a GCI score. The GCI score can be used to provide people not trained in genetics with a reliable (i.e., robust), understandable, and/or intuitive sense of what their individual risk of disease is compared to a relevant population based on current scientific research. In one embodiment a method for generating a robust GCI score for the combined effect of different loci is based on a reported individual risk for each locus studied. For example a disease or condition of interest is identified and then informational sources, including but not limited to databases, patent publications and scientific literature, are queried for information on the association of the disease of condition with one or more genetic loci. These informational sources are curated and assessed using quality criteria. In some embodiments the assessment process involves multiple steps. In other embodiments the informational sources are assessed for multiple quality criteria. The information derived from informational sources is used to identify the odds ratio or relative risk for one or more genetic loci for each disease or condition of interest.

In an alternative embodiment the odds ratio (OR) or relative risk (RR) for at least one genetic loci is not available from available informational sources. The RR is then calculated using (1) reported OR of multiple alleles of same locus, (2) allele frequencies from data sets, such as the HapMap data set, and/or (3) disease/condition prevalence from available sources (e.g., CDC, National Center for Health Statistics, etc.) to derive RR of all alleles of interest. In one embodiment the ORs of multiple alleles of same locus are estimated separately or independently. In a preferred embodiment the ORs of multiple alleles of same locus are combined to account for dependencies between the ORs of the different alleles. In some embodiments established disease models (including, but not limited to models such as the multiplicative, additive, Harvard-modified, dominant effect) are used to generate an intermediate score that represents the risk of an individual according to the model chosen.

In another embodiment a method is used that analyzes multiple models for a disease or condition of interest and which correlates the results obtained from these different models; this minimizes the possible errors that may be introduced by choice of a particular disease model. This method minimizes the influence of reasonable errors in the estimates of prevalence, allele frequencies and ORs obtained from informational sources on the calculation of the relative risk. Because of the "linearity" or monotonic nature of the effect of a prevalence estimate on the RR, there is little or no effect of incorrectly estimating the prevalence on the final rank score; provided that the same model is applied consistently to all individuals for which a report is generated.

In another embodiment a method is used that takes into account environmental/behavioral/demographic data as additional "loci." In a related embodiment such data may be obtained from informational sources, such as medical or scientific literature or databases (e.g., associations of smoking w/lung cancer, or from insurance industry health risk assessments). In one embodiment a GCI score is produced for one or more complex diseases. Complex diseases may be influenced by multiple genes, environmental factors, and their interactions. A large number of possible interactions needs to be analyzed when studying complex diseases. In one embodiment a procedure is used to correct for multiple comparisons, such as the Bonferroni correction. In an alternative embodiment the Simes's test is used to control the overall significance level (also known as the "familywise error rate") when the tests are independent or exhibit a special type of dependence (Sarkar S. (1998)). Some probability inequalities for ordered MTP2 random variables: a proof of the Simes conjecture. Ann Stat 26:494-504). Simes's test rejects the global null hypothesis that all K test-specific null hypotheses are true if $p_{(k)} \leq \alpha k/K$ for any k in 1, . . . , K. (Simes R J (1986) An improved Bonferroni procedure for multiple tests of significance. Biometrika 73:751-754.).

Other embodiments that can be used in the context of multiple-gene and multiple-environmental-factor analysis control the false-discovery rate—that is, the expected proportion of rejected null hypotheses that are falsely rejected. This approach is particularly useful when a portion of the null hypotheses can be assumed false, as in microarray studies. Devlin et al. (2003, Analysis of multilocus models of association. Genet Epidemiol 25:36-47) proposed a variant of the Benjamini and Hochberg (1995, Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B 57:289-300) step-up procedure that controls the false-discovery rate when testing a large number of possible gene×gene interactions in multilocus association studies. The Benjamini and Hochberg procedure is related to Simes's test; setting $k^* = \max k$ such that $p(k) \leq \alpha k/K$, it rejects all k* null hypotheses corresponding to $p_{(1)}, \ldots, p_{(k)}$. In fact, the Benjamini and Hochberg procedure reduces to Simes's test when all null hypotheses are true (Benjamini Y, Yekutieli D (2001) The control of the false discovery rate in multiple testing under dependency. Ann Stat 29:1165-1188).

In some embodiments an individual is ranked in comparison to a population of individuals based on their intermediate score to produce a final rank score, which may be represented as rank in the population, such as the 99^{th} percentile or 99^{th}, 98^{th}, 97^{th}, 96^{th}, 95^{th}, 94^{th}, 93^{rd}, 92^{nd}, 91^{st}, 90^{th}, 89^{th}, 88^{th}, 87^{th}, 86^{th}, 85^{th}, 84^{th}, 83^{rd}, 82^{nd}, 81^{st}, 80^{th}, 79^{th}, 78^{th}, 77^{th}, 76^{th}, 75^{th}, 74^{th}, 73^{rd}, 72^{nd}, 71^{st}, 70^{th}, 69^{th}, 65^{th}, 60^{th}, 55^{th}, 50^{h}, 45^{th}, 40^{th}, 40^{th}, 35^{th}, 30^{th}, 25^{th}, 20^{th}, 15^{th}, 10^{th}, 5^{th}, or 0^{th}. Percentile. In another embodiment the rank may score may be displayed as a range, such as the 100^{th} to 95^{th} percentile, the 95^{th} to 85^{th} percentile, the 85^{th} to 60^{th} percentile, or any subrange between the 100^{th} and 0^{th} percentile. In yet another embodiment the individual is ranked in quartiles, such as the top 75^{th} quartile, or the lowest 25^{th} quartile. In a further embodiment the individual is ranked in comparison to the mean or median score of the population.

In one embodiment the population to which the individual is compared to includes a large number of people from various geographic and ethnic backgrounds, such as a global population. In other embodiments the population to which an individual is compared to is limited to a particular geography, ancestry, ethnicity, sex, age (fetal, neonate, child, adolescent, teenager, adult, geriatric individual) disease state (such as symptomatic, asymptomatic, carrier, early-onset, late onset). In some embodiments the population to which the individual is compared is derived from information reported in public and/or private informational sources.

In one embodiment an individual's GCI score, or GCI Plus score, is visualized using a display. In some embodiments a screen (such as a computer monitor or television screen) is used to visualize the display, such as a personal portal with relevant information. In another embodiment the display is a static display such as a printed page. In one embodiment the display may include but is not limited to one or more of the following: bins (such as 1-5, 6-10, 11-15, 16-20, 21-25, 26-30, 31-35, 36-40, 41-45, 46-50, 51-55, 56-60, 61-65, 66-70, 71-75, 76-80, 82-85, 86-90, 91-95, 96-100), a color or grayscale gradient, a thermometer, a gauge, a pie chart, a histogram or a bar graph. For example, FIGS. **18** and **19** are different displays for MS and FIG. **20** is for Crohn's disease). In another embodiment a thermometer is used to display GCI score and disease/condition prevalence. In another embodiment a thermometer displays a level that changes with the reported GCI score, for example, FIGS. **15**-**17**, the color corresponds to the risk. The thermometer may display a colorimetric change as the GCI score increases (such as changing from blue, for a lower GCI score, progressively to red, for a higher GCI score). In a related embodiment a thermometer displays both a level that changes with the reported GCI score and a colorimetric change as the risk rank increases

In an alternative embodiment an individual's GCI score is delivered to an individual by using auditory feedback. In one embodiment the auditory feedback is a verbalized instruction that the risk rank is high or low. In another embodiment the auditory feedback is a recitation of a specific GCI score such as a number, a percentile, a range, a quartile or a comparison with the mean or median GCI score for a population. In one embodiment a live human delivers the auditory feedback in person or over a telecommunications device, such as a phone (landline, cellular phone or satellite phone) or via a personal portal. In another embodiment the auditory feedback is delivered by an automated system, such as a computer. In one embodiment the auditory feedback is delivered as part of an interactive voice response (IVR) system, which is a technology that allows a computer to detect voice and touch tones using a normal phone call. In another embodiment an individual may interact with a central server via an IVR system. The IVR system may respond with pre-recorded or dynamically generated audio to interact with individuals and provide them with auditory feedback of their risk rank. In one example an individual may call a number that is answered by an IVR system. After optionally entering an identification code, a security code or undergoing voice-recognition protocols the IVR system asks the subject to select options from a menu, such as a touch tone or voice menu. One of these options may provide an individual with his or her risk rank.

In another embodiment an individual's GCI score is visualized using a display and delivered using auditory feedback, such as over a personal portal. This combination may include a visual display of the GCI score and auditory feedback, which discusses the relevance of the GCI score to the individual's overall health and possible preventive measures, may be advised.

In one example the GCI score is generated using a multi-step process. Initially, for each condition to be studied, the relative risks from the odds ratios for each of the Genetic markers is calculated. For every prevalence value p=0.01, 0.02, . . . , 0.5, the GCI score of the HapMap CEU population is calculated based on the prevalence and on the HapMap allele frequency. If the GCI scores are invariant under the varying prevalence, then the only assumption taken into account is that there is a multiplicative model. Otherwise, it is determined that the model is sensitive to the prevalence. The relative risks and the distribution of the scores in the HapMap population, for any combination of no-call values, are obtained. For each new individual, the individual's score is compared to the HapMap distribution and the resulting score is the individual's rank in this population. The resolution of the reported score may be low due to the assumptions made during the process. The population will be partitioned into quantiles (3-6 bins), and the reported bin would be the one in which the individual's rank falls. The number of bins may be different for different diseases based on considerations such as the resolution of the score for each disease. In case of ties between the scores of different HapMap individuals, the average rank will be used.

In one embodiment a higher GCI score is interpreted as an indication of an increased risk for acquiring or being diagnosed with a condition or disease. In another embodiment mathematical models are used to derive the GCI score. In some embodiments the GCI score is based on a mathematical model that accounts for the incomplete nature of the underlying information about the population and/or diseases or conditions. In some embodiments the mathematical model includes certain at least one presumption as part of the basis for calculating the GCI score, wherein said presumption includes, but is not limited to: a presumption that the odds ratio values are given; a presumption that the prevalence of the condition is known; a presumption that the genotype frequencies in the population are known; and a presumption that the customers are from the same ancestry background as the populations used for the studies and as the HapMap; a presumption that the amalgamated risk is a product of the different risk factors of the individual genetic markers. In some embodiments, the GCI may also include a presumption that the multi-genotypic frequence of a genotype is the product of frequencies of the alleles of each of the SNPs or individual genetic markers (for example, the different SNPs or genetic markers are independent across the population).

The Multiplicative Model

In one embodiment a GCI score is computed under the assumption that the risk attributed to the set of Genetic markers is the product of the risks attributed to the individual Genetic markers. This means that the different Genetic markers attribute independently of the other Genetic markers to the risk of the disease. Formally, there are k Genetic markers with risk alleles $r_1, \ldots, r_k$ and non-risk alleles $n_1, \ldots, n_k$. In SNP i, we denote the three possible genotype values as r_ir_i, n_ir_i, and n_in_i. The genotype information of an individual can be described by a vector, $(g_1, \ldots, g_k)$, where g_i can be 0, 1, or 2, according to the number of risk alleles in position i. We denote by λ_1^i the relative risk of a heterozygous genotype in position i compared to a homozygous non-risk allele at the same position. In other words, we define

$$\lambda\frac{i}{1} = \frac{P(D|n_ir_i|)}{P(D|n_in_i|)}.$$

Similarly, we denote the relative risk of an r_ir_i genotype as

$$\lambda\frac{i}{2} = \frac{P(D|n_ir_i|)}{P(D|n_in_i|)}.$$

Under the multiplicative model we assume that the risk of an individual with a genotype $(g_1, \ldots, g_k)$ is

$$GCI(g_1, \ldots, g_k) = \prod_{i=1}^{k} \lambda_{g_i}^i.$$

The multiplicative model has been previously used in the literature in order to simulate case-control studies, or for visualization purposes.

Estimating the Relative Risk.

In another embodiment the relative risks for different Genetic markers are known and the multiplicative model can be used for risk assessment. However, in some embodiments involving association studies the study design prevents the reporting of the relative risks. In some case-control studies the relative risk cannot be calculated directly from the data without further assumptions. Instead of reporting the relative risks, it is customary to report the odds ratio (OR) of the genotype, which are the odds of carrying the disease given the risk genotype (either r_ir_i or n_ir_i) vs. the odds of not carrying the disease given the risk genotypes. Formally,

$$OR_i^1 = \frac{P(D|n_ir_i|)}{P(D|n_ir_i|)} \cdot \frac{1 - P(D|n_in_i|)}{1 - P(D|n_ir_i|)}$$

$$OR_i^2 = \frac{P(D|r_ir_i|)}{P(D|n_in_i|)} \cdot \frac{1 - P(D|n_in_i|)}{1 - P(D|r_ir_i|)}$$

Finding the relative risks from the odds ratio may require additional assumptions. Such as the presumption that the allele frequencies in an entire population $a=f_{n_in_i}$, $b=f_{n_ir_i}$, and $c=f_{r_ir_i}$ are known or estimated (these could be estimated from current datasets such as the HapMap dataset which includes 120 chromosomes), and/or that the prevalence of the disease p=p(D) is known. From the preceding three equations can be derived:

$$p = a \cdot P(D \mid n_in_i) + b \cdot P(D \mid n_ir_i) + c \cdot P(D \mid r_ir_i)$$

$$OR_i^1 = \frac{P(D|n_ir_i|)}{P(D|n_ir_i|)} \cdot \frac{1 - P(D|n_in_i|)}{1 - P(D|n_ir_i|)}$$

$$OR_i^2 = \frac{P(D|r_ir_i|)}{P(D|n_in_i|)} \cdot \frac{1 - P(D|n_in_i|)}{1 - P(D|r_ir_i|)}$$

By the definition of the relative risk, after dividing by the term $pP(D|n_in_i)$, the first equation can be rewritten as:

$$\frac{1}{P(D|n_in_i|)} = \frac{a + b\lambda_1^i + c\lambda_2^i}{p},$$

and therefore, the last two equations can be rewritten as:

$$OR_i^1 = \lambda_1^i \cdot \frac{(a-p) + b\lambda_1^i + c\lambda_2^i}{a + (b-p)\lambda_1^i + c\lambda_2^i} \tag{1}$$

$$OR_i^2 = \lambda_2^i \cdot \frac{(a-p) + b\lambda_1^i + c\lambda_2^i}{a + b\lambda_1^i + (c-p)\lambda_2^i}$$

Note that when a=1 (non-risk allele frequency is 1), Equation system 1 is equivalent to the Zhang and Yu formula in Zhang J and Yu K. (What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA,* 280:1690-1, 1998), which is incorporated by reference in its entirety. In contrast to the Zhang and Yu formula, some embodiments of the present invention take into consideration the allele frequency in the population, which may affect the relative risk. Further some embodiments take into account the interdependence of the relative risks. As opposed to computing each of the relative risks independently.

Equation system 1 can be rewritten as two quadratic equations, with at most four possible solutions. A gradient descent algorithm can be used to solve these equations, where the starting point is set to be the odds ratio, e.g., $\lambda_1^i = OR_1^i$, and $\lambda_2^i = OR_2^i$

For example:

$$f_1(\lambda_1,\lambda_2) = OR_i^1(a+(b-p)\lambda_1^i + c\lambda_2^i) - \lambda_1^i \cdot ((a-p)+b\lambda_1^i + c\lambda_2^i)$$

$$f_2(\lambda_1,\lambda_2) = OR_i^2(a+b\lambda_1^i + (c-p)\lambda_2^i) - \lambda_2^i \cdot ((a-p)+b\lambda_1^i + c\lambda_2^i)$$

Finding the solution of these equations is equivalent to finding the minimum of the function $g(\lambda_1, \lambda_2) = f_1(\lambda_1, \lambda_2)^2 + f_2(\lambda_1, \lambda_2)^2$.

Thus,

$$\frac{dg}{d\lambda_1} = 2f_1(\lambda_1,\lambda_2)\cdot b\cdot(\lambda_2 - OR_2) + 2f_2(\lambda_1,\lambda_2)(2b\lambda_1 + c\lambda_2 + a - OR_1 b - p + OR_1 p)$$

$$\frac{dg}{d\lambda_2} = 2f_1(\lambda_1,\lambda_2)\cdot c\cdot(\lambda_1 - OR_1) + 2f_1(\lambda_1,\lambda_2)(2c\lambda_2 + b\lambda_1 + a - OR_2 c - p + OR_2 p)$$

In this example we begin by setting $x_0 = OR_1$, $y_0 = OR_2$. We will set the values [epsilon]$=10^{-10}$ to be a tolerance constant through the algorithm. In iteration i, we define

$$\gamma = \min\left\{0.001,\ \frac{x_{i-1}}{[\text{epsilon}] + 10\left|\frac{dg}{d\lambda_1}(x_{i-1}, y_{i-1})\right|},\ \frac{y_{i-1}}{[\text{epsilon}] + 10\left|\frac{dg}{d\lambda_2}(x_{i-1}, y_{i-1})\right|}\right\}.$$

We then set

$$x_i = x_{i-1} - \gamma\frac{dg}{d\lambda_1}(x_{i-1}, y_{i-1})$$

$$y_i = y_{i-1} - \gamma\frac{dg}{d\lambda_2}(x_{i-1}, y_{i-1})$$

There iterations are repeated until $g(x_i, y_i) <$ tolerance, where tolerance is set to 10^{-7} in the supplied code.

In this example these equations give the correct solution for different values of a, b, c, p, OR_1, and OR_2. FIG. **10** Robustness of the Relative Risk Estimation.

In some embodiments the effect of different parameters (prevalence, allele frequencies, and odds ratio errors) on the estimates of the relative risks is measured. In order to measure the effect of the allele frequency and prevalence estimates on the relative risk values, the relative risk from a set of values of different odds ratios and different allele frequencies is computed (under HWE), and the results of these calculations is plotted for prevalence values ranging from 0 to 1. FIG. **10**. Additionally, for fixed values of the prevalence, the resulting relative risks can be plotted as a function of the risk-allele frequencies. FIG. **11**. In cases when p=0, $\lambda_1 = OR_1$, and $\lambda_2 = OR_2$, and when p=1, $\lambda_1 = \lambda_2 = 0$. This can be computed directly from the equations. Additionally, in some embodiments when the risk allele frequency is high, λ_1 gets closer to a linear function, and λ_2 gets closer to a concave function with a bounded second derivative. In the limit, when c=1, $\lambda_2 = OR_2 + p(1-OR_2)$, and

$$\lambda_i = OR_i - \frac{(OR_i - 1)pOR_i}{OR_2(1-p) + pOR_1}.$$

If $OR_1 \approx OR_2$ the latter is close to a linear function as well. When risk-allele frequency is low, λ_1 and λ_2 approach the behavior of the function 1/p. In the limit, when c=0,

$$\lambda_1 = \frac{OR_1}{1 - p + pOR_1},\ \lambda_2 = \frac{OR_2}{1 - p + pOR_2}.$$

This indicates that for high risk-allele frequencies, incorrect estimates of the prevalence will not significantly affect the resulting relative risk. Further, for low risk-allele frequency, if a prevalence value of $p' = \alpha p$ is substituted for the correct prevalence p, then the resulting relative risks will be off by a factor of

$$\frac{1}{\alpha}$$

at most. This is illustrated in sections (c) and (d) of FIG. **11**. Note that for high risk-allele frequencies the two graphs are quite similar and while there is a higher deviation in the difference in the values of the relative risks for low allele frequencies, this deviation is less than a factor of 2.

Calculating the GCI Score

In one embodiment the Genetic Composite Index is calculated by using a reference set that represents the relevant population. This reference set may be one of the populations in the HapMap, or anther genotype dataset.

In this embodiment the GCI is computed as follows. For each of the k risk loci, the relative risk is calculated from the odds ratio using the equation system 1. Then, the multiplicative score for each individual in the reference set is calculated. The GCI of an individual with a multiplicative score of s is the fraction of all individuals in the reference dataset with a score of s'≤s. For instance, if 50% of the individuals in the reference set have a multiplicative score smaller than s, the final GCI score of the individual would be 0.5.

Other Models

In one embodiment the multiplicative model is used. In alternative embodiments other models that may be used for the purpose of determining the GCI score. Other suitable models include but are not limited to:

The Additive Model. Under the additive model the risk of an individual with a genotype ($g_1, \ldots, g_k$) is presumed to be

$$GCI(g_1, \ldots, g_k) = \sum_{i=1}^{k} \lambda^i_{g_i}.$$

Generalized Additive Model. Under the generalized additive model it is presumed that there is a function f such that the risk of an individual with a genotype ($g_1, \ldots, g_k$) is

$$GCI(g_1, \ldots, g_k) = \sum_{i=1}^{k} f(\lambda^i_{g_i}).$$

Harvard Modified Score (Het). This score was derived from G. A Colditz et al., so that the score that applies to genetic markers (Harvard report on cancer prevention volume 4: Harvard cancer risk index. *Cancer Causes and Controls,* 11:477-488, 2000 which is herein incorporated in its entirety). The Het score is essentially a generalized additive score, although the function f operates on the odds ratio values instead of the relative risks. This may be useful in cases where the relative risk is difficult to estimate. In order to define the function f, an intermediate function g, is defined as:

$$g(x) = \begin{cases} 0 & 1 < x \le 1.09 \\ 5 & 1.09 < x \le 1.49 \\ 10 & 1.49 < x \le 2.99 \\ 25 & 2.99 < x \le 6.99 \\ 50 & 6.99 < x \end{cases}$$

Next the quantity

$$het = \sum_{i=1}^{k} p^i_{het} g(OR^i_1)$$

is calculated, where p_{het}^{i} is the frequency of heterozygous individuals in SNP i across the reference population. The function f is then defined as $f(x)=g(x)/het$, and the Harvard Modified Score (Het) is simply defined as

$$\sum_{i=1}^{k} f(OR^i_{g_i}).$$

The Harvard Modified Score (Hom). This score is similar to the Het score, except that the value het is replaced by the value

$$hom = \sum_{i=1}^{k} p^i_{hom} g(OR^i_1),$$

where p_{hom}^{i} is the frequency of individuals with homozygous risk-allele.

The Maximum-Odds Ratio. In this model, it is presumed that one of the Genetic markers (one with a maximal odds ratio) gives a lower bound on the combined risk of the entire panel. Formally, the score of an individual with genotypes ($g_1, \ldots, g_k$) is $GCI(g_1, \ldots, g_k)=\max_{i=1}^{k} OR_{g_i}^{i}$.

A Comparison between the Scores

In one Example the GCI score was calculated based on multiple models across the HapMap CEU population, for 10 SNPs associated with T2D. The relevant SNPs were rs7754840, rs4506565, rs7756992, rs10811661, rs12804210, rs8050136, rs1111875, rs4402960, rs5215, rs1801282. For each of these SNPs, an odds ratio for three possible genotypes is reported in the literature. The CEU population consists of thirty mother-father-child trios. Sixty parents from this population were used in order to avoid dependencies. One of the individuals that had a no-call in one of the 10 SNPs was excluded, resulting in a set of 59 individuals. The GCI rank for each of the individuals was then calculated using several different models.

It was observed that for this dataset different models produced highly correlated results. FIGS. **12** & **13**. The Spearman correlation was calculated between each pair of models (Table 2), which showed that the Multiplicative and Additive model had a correlation coefficient of 0.97, and thus the GCI score would be robust using either the additive or multiplicative models. Similarly, the correlation between the Harvard modified scores and the multiplicative model was 0.83, and the correlation coefficient between the Harvard scores and the additive model was 0.7. However, using the maximum odds ratio as the genetic score yielded a dichotomous score which was defined by one SNP. Overall these results indicate score ranking provided a robust framework that minimized model dependency.

TABLE 2

The Spearman correlations for the score distributions on the CEU data between model pairs.

	Multiplicative	Additive	Harv-Het	Harv-Hom	MAX OR
Mult	1	0.97	0.83	0.83	0.42
Additive	0.97	1.	0.7	0.7	0.6
Harv-Het	0.83	0.7	1	1	0
Harv-Hom	0.83	0.7	1	1	0
MAX OR	0.42	0.6	0	0	1

The effect of variation in the prevalence of T2D on the resulting distribution was measured. The prevalence values from 0.001 to 0.512 was varied (FIG. **14**). For the case of T2D, it was observed that different prevalence values result in the same order of individuals (Spearman correlation>0.99), therefore an artificially fixed value of prevalence 0.01 could be presumed.

Extending the Model to an Arbitrary Number of Variants

In another embodiment the model can be extended to the situations where an arbitrary number of possible variants occur. Previous considerations dealt with situations where there were three possible variants (nn, nr, rr). Generally, when a multi-SNP association is known, an arbitrary number of variants may be found in the population. For example, when an interaction between two Genetic markers is associated with a condition, there are nine possible variants. This results in eight different odds ratios values.

To generalize the initial formula, it may be assumed that there are k+1 possible variants $\alpha_0, \ldots, \alpha_k$, with frequencies $f_0, f_1, \ldots, f_k$, measured odds ratios of $1, OR_1, \ldots, OR_k$, and unknown relative risk values $1, \lambda_1, \ldots, \lambda_k$. Further it may be assumed that all relative risks and odds ratios are measured with respect to α_0, and thus,

$$\lambda_i = \frac{P(D \mid a_i)}{P(D \mid a_o)}, \quad \text{and } OR_i = \frac{P(D \mid a_i)}{P(D \mid a_o)} \cdot \frac{1 - P(D \mid a_i)}{1 - P(D \mid a_o)}.$$

Based on:

$$p = \sum_{i=0}^{k} f_i P(D \mid a_i),$$

It is determined that

$$OR_i = \lambda_i \frac{\sum_{i=0}^{k} f_i \lambda_i - p}{\sum_{i=0}^{k} f_i \lambda_i - \lambda_i p}.$$

Further if it is set that

$$C = \sum_i f_i \lambda_i,$$

this results in the equation:

$$\lambda_i = \frac{C \cdot OR_i}{C - p + OR_i p},$$

and thus,

$$C = \sum_{i=0}^{k} f_i \lambda_i = \sum_{i=0}^{k} \frac{C \cdot OR_i f_i}{C - p + OR_i p},$$

or

$$1 = \sum_{i=0}^{k} \frac{OR_i f_i}{C - p + OR_i p}.$$

The latter is an equation with one variable (C). This equation can produce many different solutions (essentially, up to k+1 different solutions). Standard optimization tools such as gradient descent can be used to find the closest solution to $C_0 = \Sigma f_i t_i$.

The present invention uses a robust scoring framework for the quantification of risk factors. While different genetic models may result in different scores, the results are usually correlated. Therefore the quantification of risk factors is generally not dependent on the model used.

Estimating Relative Risk Case Control Studies

A method that estimates the relative risks from the odds ratios of multiple alleles in a case-control study is also provided in the present invention. In contrast to previous approaches, the method takes into consideration the allele frequencies, the prevalence of the disease, and the dependencies between the relative risks of the different alleles. The performance of the approach on simulated case-control studies was measured, and found to be extremely accurate.

Methods

In the case where a specific SNP is tested for association with a disease D, R and N denote the risk and non-risk alleles of this particular SNP. P(RR|D), P(RN|D) and P(NN|D) denote the probability of getting affected by the disease given that a person is homozygous for the risk allele, heterozygous, or homozygous for the non-risk allele respectively. f_{RR}, f_{RN} and f_{NN} are used to denote the frequencies of the three genotypes in the population. Using these definitions, the relative risks are defined as

$$\lambda_{RR} = \frac{P(D \mid RR)}{P(D \mid NN)}$$

$$\lambda_{RN} = \frac{P(D \mid RN)}{P(D \mid NN)}$$

In a case-control study, the values P(RR|D), P(RR|~D) can be estimated, i.e., the frequency of RR among the cases and the controls, as well as P(RN|D), P(RN|~D), P(NN|D), and P(NN|~D), i.e., the frequency of RN and NN among the cases and the controls. In order to estimate the relative risk, Bayes law can be used to get:

$$\lambda_{RR} = \frac{P(RR \mid D) f_{NN}}{P(NN \mid D) f_{RR}}$$

$$\lambda_{RN} = \frac{P(D \mid RN) f_{NN}}{P(D \mid NN) f_{RR}}$$

Thus, if the frequencies of the genotypes are known, one can use those to calculate the relative risks. The frequencies of the genotypes in the population cannot be calculated from the case-control study itself, since they depend on the prevalence of disease in the population. In particular, if the prevalence of the disease is p(D), then:

$$f_{RR} = P(RR|D)p(D) + P(RR|{\sim}D)(1-p(D))$$

$$f_{RN} = P(RN|D)p(D) + P(RN|{\sim}D)(1-p(D))$$

$$f_{NN} = P(NN|D)p(D) + P(NN|{\sim}D)(1-p(D))$$

When p(D) is small enough, the frequencies of the genotypes can be approximated by the frequencies of the genotypes in the control population, but this would not be an accurate estimate when the prevalence is high. However, if a reference dataset is given (e.g., the HapMap [cite]), one can estimate the genotype frequencies based on the reference dataset.

Most current studies do not use a reference dataset to estimate the relative risk, and only the odds-ratio is reported. The odds-ratio can be written as

$$OR_{RR} = \frac{P(RR \mid D) P(NN \mid \sim D)}{P(NN \mid D) P(RR \mid \sim D)}$$

-continued

$$OR_{RN} = \frac{P(RN \mid D)P(NN \mid \sim D)}{P(NN \mid D)P(RN \mid \sim D)}$$

The odds ratios are typically advantageous since there is usually no need to have an estimate of the allele frequencies in the population; in order to calculate the odds ratios typically what is needed is the genotype frequencies in the cases and in the controls.

In some situations, the genotype data itself is not available, but the summary data, such as the odds-ratios are available. This is the case when meta-analysis is being performed based on results from previous case-control studies. In this case, how to find the relative risks from the odds ratios is demonstrated. Using the fact that the following equation holds:

$$p(D)=f_{RR}P(D|RR)+f_{RN}P(D|RN)+f_{NN}P(D|NN)$$

If this equation is divided by P(D|NN), we get

$$\frac{p(D)}{p(D \mid NN)} = f_{RR}\lambda_{RR} + f_{RN}\lambda_{RN} + f_{NN}$$

This allows the odds ratios to be written in the following way:

$$\begin{aligned} OR_{RR} &= \frac{P(D \mid RR)(1 - P(D \mid NN))}{P(D \mid NN)(1 - P(D \mid RR))} \\ &= \lambda_{RR}\frac{\frac{p(D)}{p(D \mid NN)} - p(D)}{\frac{p(D)}{p(D \mid NN)} - p(D)\lambda_{RR}} \\ &= \lambda_{RR}\frac{f_{RR}\lambda_{RR} + f_{RN}\lambda_{RN} + f_{NN} - p(D)}{f_{RR}\lambda_{RR} + f_{RN}\lambda_{RN} + f_{NN} - p(D)\lambda_{RR}} \end{aligned}$$

By a similar calculation, the following system of equations results:

$$\begin{aligned} OR_{RR} &= \lambda_{RR}\frac{f_{RR}\lambda_{RR} + f_{RN}\lambda_{RN} + f_{NN} - p(D)}{f_{RR}\lambda_{RR} + f_{RN}\lambda_{RN} + f_{NN} - p(D)\lambda_{RR}} \\ OR_{RN} &= \lambda_{RN}\frac{f_{RR}\lambda_{RR} + f_{RN}\lambda_{RN} + f_{NN} - p(D)}{f_{RR}\lambda_{RR} + f_{RN}\lambda_{RN} + f_{NN} - p(D)\lambda_{RN}} \end{aligned} \quad \text{Equation 1}$$

If the odds-ratios, the frequencies of the genotypes in the populations, and the prevalence of the disease are known, the relative risks can be found by solving this set of equations.

Note that these are two quadratic equations, and thus they have a maximum of four solutions. However, as shown below that there is typically one possible solution to this equation.

Note that when $f_{NN}=1$, Equation system 1 is equivalent to the Zhang and Yu formula; however, here the allele frequency in the population is taken into account. Furthermore, our method takes into account the fact that the two relative risks depend on each other, while previous methods suggest to compute each of the relative risks independently.

Relative risks for multi-allelic loci. If multi-markers or other multi-allelic variants are considered, the calculation is complicated slightly. $a_0, a_1, \ldots, a_k$ is denoted by the possible k+1 alleles, where a_0 is the non-risk allele. Allele frequencies $f_0, f_1, f_2, \ldots, f_k$ in the population for the k+1 possible alleles are assumed. For allele i, the relative risk and odds-ratios are defined as

$$\lambda_i = \frac{P(D \mid a_i)}{P(D \mid a_0)}$$

$$OR_i = \frac{P(D \mid a_i)(1 - P(D \mid a_0))}{P(D \mid a_0)(1 - P(D \mid a_i))} = \lambda_i\frac{1 - P(D \mid a_0)}{1 - P(D \mid a_i)}$$

The following equation holds for the prevalence of the disease:

$$p(D) = \sum_{i=0}^{k} f_i P(D \mid a_i)$$

Thus, by dividing both sides of the equation by $p(D|a_0)$, we get:

$$\frac{p(D)}{p(D \mid a_0)} = \sum_{i=0}^{k} f_i\lambda_i$$

Resulting in:

$$OR_i = \lambda_i\frac{\sum_{i=0}^{k} f_i\lambda_i - p(D)}{\sum_{i=0}^{k} f_i\lambda_i - \lambda_i p(D)},$$

By setting

$$C = \sum_{i=0}^{k} f_i\lambda_i,$$

the result is

$$\lambda_i = C \cdot \frac{OR_i}{p(D)OR_i + C - p(D)}.$$

Thus, by the definition of C, it is:

$$1 = \sum_{i=0}^{k} f_i\frac{\lambda_i}{C} = \sum_{i=0}^{k} \frac{f_i OR_i}{p(D)OR_i + C - p(D)}.$$

This is a polynomial equation with one variable C. Once C is determined, the relative risks are determined. The polynomial is of degree k+1, and thus we expect to have at most k+1 solutions. However, since the right-hand side of the equation is a strictly decreasing as a function of C, there can typically only be one solution to this equation. Finding this solution is easy using a binary search, since the solution is bounded between C=1 and

$$C=\sum_{i=0}^{k} OR_i.$$

Robustness of the Relative Risk Estimation. The effect of each of the different parameters (prevalence, allele frequencies, and odds ratio errors) on the estimates of the relative risks was measured. In order to measure the effect of the allele frequency and prevalence estimates on the relative risk values, the relative risk was calculated from a set of values of different odds ratios, different allele frequencies (under HWE), and plotted the results of these calculations for a prevalence values ranging from 0 to 1.

Additionally, for fixed values of the prevalence, the resulting relative risks as a function of the risk-allele frequencies was plotted. Evidently, in all cases when p(D)=0, $\lambda_{RR}=OR_{RR}$, and $\lambda_{RN}=OR_{RN}$, and when p(D)=1, $\lambda_{RR}=\lambda_{RN}=0$. This can be computed directly from Equation 1. Additionally, when the risk allele frequency is high, λ_{RR} approaches a linear behavior, and λ_{RN} approaches a concave function with a bounded second derivative. When the risk-allele frequency is low, λ_{RR} and λ_{RN} approach the behavior of the function 1/p(D). This means that for high risk-allele frequency, wrong estimates of the prevalence will not affect the resulting relative risk by much.

The following examples illustrate and explain the invention. The scope of the invention is not limited by these examples.

Example I

Generation and Analysis of SNP Profile

The individual is provided a sample tube in the kit, such as that available from DNA Genotek, into which the individual deposits a sample of saliva (approximately 4 mls) from which genomic DNA will be extracted. The saliva sample is sent to a CLIA certified laboratory for processing and analysis. The sample is typically sent to the facility by overnight mail in a shipping container that is conveniently provided to the individual in the collection kit.

In a preferred embodiment, genomic DNA is isolated from saliva. For example, using DNA self collection kit technology available from DNA Genotek, an individual collects a specimen of about 4 ml saliva for clinical processing. After delivery of the sample to an appropriate laboratory for processing, DNA is isolated by heat denaturing and protease digesting the sample, typically using reagents supplied by the collection kit supplier at 50° C. for at least one hour. The sample is next centrifuged, and the supernatant is ethanol precipitated. The DNA pellet is suspended in a buffer appropriate for subsequent analysis.

The individual's genomic DNA is isolated from the saliva sample, according to well known procedures and/or those provided by the manufacturer of a collection kit. Generally, the sample is first heat denatured and protease digested. Next, the sample is centrifuged, and the supernatant is retained. The supernatant is then ethanol precipitated to yield a pellet containing approximately 5-16 ug of genomic DNA. The DNA pellet is suspended in 10 mM Tris pH 7.6, 1 mM EDTA (TE). A SNP profile is generated by hybridizing the genomic DNA to a commercially available high density SNP array, such as those available from Affymetrix or Illumina, using instrumentation and instructions provided by the array manufacturer. The individual's SNP profile is deposited into a secure database or vault.

The patient's data structure is queried for risk-imparting SNPs by comparison to a clinically-derived database of established, medically relevant SNPs whose presence in a genome correlates to a given disease or condition. The database contains information of the statistical correlation of particular SNPs and SNP haplotypes to particular diseases or conditions. For example, as shown in Example III, polymorphisms in the apolipoprotein E gene give rise to differing isoforms of the protein, which in turn correlate with a statistical likelihood of developing Alzheimer's Disease. As another example, individuals possessing a variant of the blood clotting protein Factor V known as Factor V Leiden have an increased tendency to clot. A number of genes in which SNPs have been associated to a disease or condition phenotype are shown in Table 1. The information in the database is approved by a research/clinical advisory board for its scientific accuracy and importance, and may be reviewed with governmental agency oversight. The database is continually updated as more SNP-disease correlations emerge from the scientific community.

The results of the analysis of an individual's SNP profile is securely provided to patient by an on-line portal or mailings. The patient is provided interpretation and supportive information, such as the information shown for Factor V Leiden in Example IV. Secure access to the individual's SNP profile information, such as through an on-line portal, will facilitate discussions with the patient's physician and empower individual choices for personalized medicine.

Example II

Update of Genotype Correlations

In response to a request for an initial determination of an individual's genotype correlations, a genomic profile is generated, genotype correlations are made, and the results are provided to the individual as described in Example I. Following an initial determination of an individual's genotype correlations, subsequent, updated correlations are or can be determined as additional genotype correlations become known. The subscriber has a premium level subscription and their genotype profile and is maintained in a secure database. The updated correlations are performed on the stored genotype profile.

For example, an initial genotype correlation, such as described above in Example I, could have determined that a particular individual does not have ApoE4 and thus is not predisposed to early-onset Alzheimer's Disease, and that this individual does not have Factor V Leiden. Subsequent to this initial determination, a new correlation could become known and validated, such that polymorphisms in a given gene, hypothetically gene XYZ, are correlated to a given condition, hypothetically condition 321. This new genotype correlation is added to the master database of human genotype correlations. An update is then provided to the particular individual by first retrieving the relevant gene XYZ data from the particular individual's genomic profile stored in a secure database. The particular individual's relevant gene XYZ data is compared to the updated master database information for gene XYZ. The particular individual's susceptibility or genetic predisposition to condition 321 is determined from this comparison. The results of this determination are added to the particular individual's genotype correlations. The updated results of whether or not the particular individual is susceptible or genetically predisposed to condition 321 is provided to the particular individual, along with interpretative and supportive information.

Example III

Correlation of ApoE4 Locus and Alzheimer's Disease

The risk of Alzheimer's disease (AD) has been shown to correlate with polymorphisms in the apolipoprotein E (APOE) gene, which gives rise to three isoforms of APOE referred to as ApoE2, ApoE3, and ApoE4. The isoforms vary from one another by one or two amino acids at residues 112 and 158 in the APOE protein. ApoE2 contains 112/158 cys/cys; ApoE3 contains 112/158 cys/arg; and ApoE4 contains 112/158 arg/arg. As shown in Table 3, the risk of Alzheimer's disease onset at an earlier age increases with the number of APOE ϵ4 gene copies. Likewise, as shown in Table 3, the relative risk of AD increases with number of APOE ϵ4 gene copies.

TABLE 3

Prevalence of AD Risk Alleles (Corder et al., Science: 261: 921-3, 1993)

APOE ϵ4 Copies	Prevalence	Alzheimer's Risk	Onset Age
0	73%	20%	84
1	24%	47%	75
2	3%	91%	68

TABLE 4

Relative Risk of AD with ApoE4 (Farrer et al., JAMA: 278: 1349-56, 1997)

APOE Genotype	Odds Ratio
ϵ2ϵ2	0.6
ϵ2ϵ3	0.6
ϵ3ϵ3	1.0
ϵ2ϵ4	2.6
ϵ3ϵ4	3.2
ϵ4ϵ4	14.9

Example IV

Information for Factor V Leiden Positive Patient

The following information is exemplary of information that could be supplied to an individual having a genomic SNP profile that shows the presence of the gene for Factor V Leiden. The individual may have a basic subscription in which the information may be supplied in an initial report.

What is Factor V Leiden?

Factor V Leiden is not a disease, it is the presence of a particular gene that is passed on from one's parents. Factor V Leiden is a variant of the protein Factor V (5) which is needed for blood clotting. People who have a Factor V deficiency are more likely to bleed badly while people with Factor V Leiden have blood that has an increased tendency to clot.

People carrying the Factor V Leiden gene have a five times greater risk of developing a blood clot (thrombosis) than the rest of the population. However, many people with the gene will never suffer from blood clots. In Britain and the United States, 5 percent of the population carry one or more genes for Factor V Leiden, which is far more than the number of people who will actually suffer from thrombosis.

How do You get Factor V Leiden?

The genes for the Factor V are passed on from one's parents. As with all inherited characteristics, one gene is inherited from the mother and one from the father. So, it is possible to inherit: —two normal genes or one Factor V Leiden gene and one normal gene -or two Factor V Leiden genes. Having one Factor V Leiden gene will result in a slightly higher risk of developing a thrombosis, but having two genes makes the risk much greater.

What are the Symptoms of Factor V Leiden?

There are no signs, unless you have a blood clot (thrombosis).

What are the Danger Signals?

The most common problem is a blood clot in the leg. This problem is indicated by the leg becoming swollen, painful and red. In rarer cases a blood clot in the lungs (pulmonary thrombosis) may develop, making it hard to breathe. Depending on the size of the blood clot this can range from being barely noticeable to the patient experiencing severe respiratory difficulty. In even rarer cases the clot might occur in an arm or another part of the body. Since these clots formed in the veins that take blood to the heart and not in the arteries (which take blood from the heart), Factor V Leiden does not increase the risk of coronary thrombosis.

What can be Done to Avoid Blood Clots?

Factor V Leiden only slightly increases the risk of getting a blood clot and many people with this condition will never experience thrombosis. There are many things one can do to avoid getting blood clots. Avoid standing or sitting in the same position for long periods of time. When traveling long distances, it is important to exercise regularly—the blood must not 'stand still'. Being overweight or smoking will greatly increase the risk of blood clots. Women carrying the Factor V Leiden gene should not take the contraceptive pill as this will significantly increase the chance of getting thrombosis. Women carrying the Factor V Leiden gene should also consult their doctor before becoming pregnant as this can also increase the risk of thrombosis.

How does a Doctor Find Out if You have Factor V Leiden?

The gene for Factor V Leiden can be found in a blood sample.

A blood clot in the leg or the arm can usually be detected by an ultrasound examination.

Clots can also be detected by X-ray after injecting a substance into the blood to make the clot stand out. A blood clot in the lung is harder to find, but normally a doctor will use a radioactive substance to test the distribution of blood flow in the lung, and the distribution of air to the lungs. The two patterns should match—a mismatch indicates the presence of a clot.

How is Factor V Leiden Treated?

People with Factor V Leiden do not need treatment unless their blood starts to clot, in which case a doctor will prescribe blood-thinning (anticoagulant) medicines such as warfarin (e.g. Marevan) or heparin to prevent further clots. Treatment will usually last for three to six months, but if there are several clots it could take longer. In severe cases the course of drug treatment may be continued indefinitely; in very rare cases the blood clots may need to be surgically removed.

How is Factor V Leiden Treated during Pregnancy?

Women carrying two genes for Factor V Leiden will need to receive treatment with a heparin coagulant medicine during pregnancy. The same applies to women carrying just one gene for Factor V Leiden who have previously had a blood clot themselves or who have a family history of blood clots.

All women carrying a gene for Factor V Leiden may need to wear special stockings to prevent clots during the last half of pregnancy. After the birth of the child they may be prescribed the anticoagulant drug heparin.

Prognosis

The risk of developing a clot increases with age, but in a survey of people over the age of 100 who carry the gene, it was found that only a few had ever suffered from thrombosis. The National Society for Genetic Counselors (NSGC) can provide a list of genetic counselors in your area, as well as information about creating a family history. Search their online database at www.nsgc.org/consumer.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

We claim:

1. A method of generating at least one Genetic Composite Index (GCI) score, wherein said GCI score represents an estimation of an individual's risk to a phenotype comprising:

a) obtaining a genetic sample from said individual;

b) generating a genomic profile from said genetic sample;

c) determining at least two relative risks (RR) or odds ratios (OR) for a phenotype by comparing said individual's genomic profile to a current database of human genotype correlations wherein a human genotype correlation is a correlation between a genetic variant and a phenotype, wherein phenotype is selected from Alzheimers (AD), colorectal cancer (CRC), osteoarthritis (OA), exfoliation glaucoma (XFG), obesity (BMIOB), Graves Disease (GD), hemochromatosis (HEM), myocardial infarction (MI), multiple sclerosis (MS), psoriasis (PS), restless legs syndrome (RLS), celiac disease (CelD), prostate cancer (PC), lupus (SLE), macular degeneration (AMD), rheumatoid arthritis (RA), breast cancer (BC), Crohn's disease (CD), Type 2 diabetes (T2D), and a combination thereof, wherein the RR or OR are determined by

$$OR_i^1 = \frac{P(D|n_i r_i|)}{P(D|n_i r_i|)} \cdot \frac{1 - P(D|n_i n_i|)}{1 - P(D|n_i r_i|)};$$

and wherein the genomic variant is selected from SNP is:rs4420638 when said phenotype is AD; rs6983267 when said phenotype is CRC; rs4911178 when said phenotype is OA; rs2165241 when said phenotype is XFG; rs9939609 or rs9291171 when said phenotype is BMIOB; rs3087243, DRBI*0301 DQA1*0501 when said phenotype is GD; rs1800562 or rs129128 when said phenotype is HEM; rs1866389, rs1333049, or rs6922269 when said phenotype is MI; rs6897932, rs12722489, or DRB1*1501 when said phenotype is MS; rs6859018, rs11209026, or HLAC*0602 when said phenotype is PS; rs6904723, rs2300478, rs1026732, or rs9296249 when said phenotype is RLS; rs6840978, rs11571315, rs2187668, or DQA1*0301 DQB1*0302 when said phenotype is CelD; rs4242384, rs6983267, rs16901979, rs17765344, or rs4430796 when said phenotype is PC; rs12531711, rs10954213, rs2004640, DRB1*0301, or DRB1*1501 when said phenotype is SLE; rs10737680, rs10490924, rs541862, rs2230199, rs1061170, or rs9332739 when said phenotype is AMD; rs6679677, rs11203367, rs6457617, DRB*0101, DRB1*0401, or DRB1*0404 when said phenotype is RA; rs3803662, rs2981582, rs4700485, rs3817198, rs17468277, rs6721996, or rs3803662 when said phenotype is BC; rs2066845, rs5743293, rs10883365, rs17234657, rs10210302, rs9858542, rs11805303, rs1000113, rs17221417, rs2542151, or rs10761659 when said phenotype is CD; rs13266634, rs4506565, rs10012946, rs7756992, rs10811661, rs12288738, rs8050136, rs1111875, rs4402960, rs5215, or rs1801282 when said phenotype is T2D;

d) calculating at least one GCI score from said at least two relative risks or odds ratios using

$$GCI(g_1, \ldots, g_k) = \prod_{i=1}^{k} \lambda_{g_i}^{i};$$

e) reporting said at least one GCI score; and

f) providing genetic counseling to the individual based on said at least one GCI score.

2. The method of claim **1**, wherein a third party obtains said genetic sample.

3. The method of claim **1**, wherein said generating of a genomic profile is by a third party.

4. The method of claim **1**, wherein said reporting comprises transmission of said results over a network.

5. The method of claim **1**, wherein said genomic profile is of said individual's entire genome.

6. The method of claim **1**, wherein said method comprises determining said at least two relative risks or odds ratios from 10 or more genotype correlations.

7. The method of claim **1**, further comprising generating a GCI Plus score.

8. The method of claim **1**, wherein said genetic sample is from a biological sample selected from said group consisting of blood, hair, skin, saliva, semen, urine, fecal material, sweat, and buccal sample.

9. The method of claim **1**, wherein said genotype correlations are correlations of single nucleotide polymorphisms to phenotypes that are not medical conditions.

10. The method of claim **1**, wherein said genomic profile is generated using a high density DNA microarray, DNA sequencing, or PCR based method.

11. The method of claim **1**, wherein said results further comprises incorporating a characteristic of said individual selected from physical data, medical data, demographic data, exposure data, lifestyle data, behavior data, ethnicity, ancestry, geography, gender, age, family history, and previously determined phenotypes.

12. The method of claim **1**, wherein said genomic profile comprises a genetic marker in linkage disequilibrium with a genetic variant correlated with a phenotype.

13. The method of claim **1**, wherein said GCI score is an estimated lifetime risk.

14. The method of claim **1**, wherein said genomic profile comprises at least 100,000 genetic variants.

15. The method of claim **1**, wherein said genomic profile comprises at least 400,000 genetic variants.

16. The method of claim **1**, further comprising reporting information on said phenotype, wherein said information is selected from the group consisting of: prevention strategy, wellness information, therapy, symptom awareness, early detection scheme, intervention scheme, and refined identification and sub-classification of said phenotype.

17. The method of claim **11**, wherein said individual's physical data is selected from the group consisting of: blood pressure, heart rate, glucose level, metabolite level, ion level, weight, height, cholesterol level, vitamin level, blood cell count, body mass index (BMI), protein level, and transcript level.

18. The method of claim **1**, further comprising:

f) updating said database with at least one human genotype correlation;

g) generating at least one additional relative risk or odds ratio for said phenotype by comparing said individual's genomic profile to said at least one human genotype correlation of step f);

h) calculating at least one updated Genetic Composite Index (GCI) from said at least one additional relative risk or odds ratio determined in step g); and,

i) reporting said results from step h) to said individual or a health care manager of said individual.

19. The method of claim **1**, wherein the reporting of said at least one GCI score comprises electronic transmission.

20. The method of claim **19**, wherein the reporting comprises transmission of said at least one GCI score via an online portal.

21. The method of claim **19**, wherein the reporting comprises transmission of said at least one GCI score over a network.

* * * * *